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## Original Communications

### THE RELATION OF VITAMIN B<sub>1</sub> TO THE REPRODUCTIVE CYCLE\*

CORRELATION BETWEEN VITAMIN B<sub>1</sub> CONTENT OF DIET AND ELECTRO-  
CARDIOGRAPHIC FINDINGS IN 91 PREGNANT WOMEN

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THE story of vitamin B<sub>1</sub> is an interesting chapter in medical science<sup>1</sup> and covers the notable discovery of Eijkman,<sup>2</sup> the researches of Funk,<sup>3</sup> Jansen and Donath,<sup>4</sup> and, more recently, the complete synthesis of thiamin by Williams and Cline.<sup>5</sup> The chemical structure of vitamin B<sub>1</sub> (thiamin) is now known, and it has been isolated in the form of its chloride hydrochloride.

The international unit of vitamin B<sub>1</sub> has been defined (1938) as the antineuritic activity of 3 micrograms of the international standard preparation of crystalline vitamin B<sub>1</sub> hydrochloride. One milligram of thiamin chloride is equivalent to 333 international units of vitamin B<sub>1</sub>. The Council on Pharmacy and Chemistry of the American Medical Association has allowed certain claims for thiamin chloride, and practically all these may find place in obstetric practice.

It is generally accepted that this dietary essential has an important role in the functioning of every cell, rather than in the activity of a special organ or tissue system.<sup>6</sup> Storage of vitamin B<sub>1</sub> appears to be of a limited order. The heart, liver, and kidney of experimental animals apparently have the highest content<sup>7, 8</sup> under normal conditions and,

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within certain limits, this is undoubtedly influenced by the amount of vitamin in the diet.<sup>9</sup> Vitamin B<sub>1</sub> cannot be synthesized in the normal processes of the human body.

The dependence of the urinary excretion of vitamin B<sub>1</sub> upon the dietary intake has been investigated by several workers.<sup>10, 11</sup> Robinson and his co-workers found recently that urinary excretion levels can, under proper conditions, be used as an index of thiamin nutrition in human beings. They also reported good correlation between urinary thiamin excretion and the adequacy of vitamin B<sub>1</sub> in the preceding diet. Deficiency symptoms of nutritional origin have been found associated with low excretion levels, and with poor excretion response to test doses. With suitable practical methods, the concentration of vitamin B<sub>1</sub> in the body tissues, blood and excretory products may be determined; and requirements necessary to maintain normal health or to treat deficiency diseases in the human being may be established. At present clinical response is the best test for adequacy of dosage in such conditions.

Vitamin B<sub>1</sub> is associated with the intermediary metabolism of carbohydrates.<sup>12, 13</sup> The pyrophosphoric acid ester of vitamin B<sub>1</sub> acts as a co-enzyme (co-carboxylase) to activate carboxylase which catalyzes pyruvic acid, a conversion product of lactic acid. If the pyruvic acid is destroyed by oxidation, the presence of co-carboxylase is again necessary as it acts here as a co-ferment with oxidase.

The need of an increased intake for growth of young rats has been demonstrated, as well as a similar need in female rats at puberty. The gastrointestinal tract responds to a vitamin B<sub>1</sub> deficiency with an anorexia, a depression of the acid secreting response of the gastric glands, and an atony of the intestines.

In the physiology of the heart muscle, Weiss and Wilkins<sup>14</sup> point out that thiamin chloride acts as an acceptor, causing the oxygen to unite with the carbohydrate and amino acids delivered to the cell by the blood and lymphatic circulation, increasing the rate of intracellular metabolism, so that the metabolic process is nearer to the end point of the cell oxidation process.

The best animal sources<sup>15</sup> of vitamin B<sub>1</sub> include pork, other muscle and organ foods, while egg yolk, chicken, fish, and milk are poor sources, but milk may be regarded as an important source of supply, since it need not be processed, and because it is usually used in fair quantities. The richest vegetable supply lies in whole grain cereals, legumes, and nuts. While other vegetables, including potatoes, may be fair sources of vitamin B<sub>1</sub>, the usual disregard of nutrient losses in cooking causes them frequently to be depreciated markedly in value. Although fruits in general have a low content, the fact that they are eaten raw serves to offset any possible loss in cooking. Not alone is the manner of cooking an element in producing vitamin B<sub>1</sub> deficiency, but the processing of the generally used white flour removes a large available amount through loss of wheat germ and bran which normally make whole grain one of the most important sources of supply.

The modern American diet has been regarded as deficient in many respects, due in part to faulty dietary habits and food selections based largely on appearance or taste, often leading to a high carbohydrate intake and an excess of fat. Again, economic status plays a part and, in an effort to provide sufficient calories in energy foods at low cost, a carbohydrate diet prevails. Voluntary faddish restrictions in diet, for supposed allergies, for weight reduction, or through misleading advice, lead to marked inadequacies in dietary essentials. Organic or functional disease may interfere with both absorption and utilization and bring to light latent deficiency conditions.

Stiebeling and Phipard,<sup>16</sup> in their analysis of diets of families of employed wage earners in eight major geographic areas of the United States, have de-

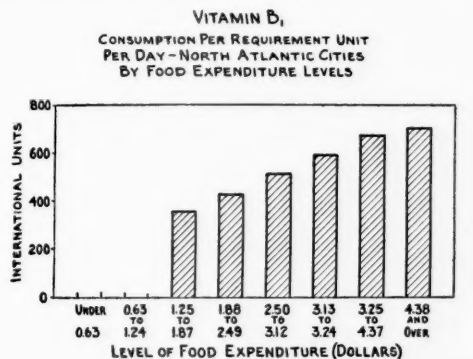


terminated the vitamin B<sub>1</sub> content. The average vitamin B<sub>1</sub> content of these diets gradually increases with rising weekly expenditures for food. Since both Pittsburgh and Philadelphia are included in Stiebeling and Phipard's North Atlantic area, the observations for this area alone will be considered (Fig. 1).

With food expenditures of \$1.25 to \$1.87 per capita per week, the average vitamin B<sub>1</sub> content of food per person reached only 290 international units. It was not until the food cost reached an expenditure of \$3.13 to \$3.74 that the allowance of 500 international units was reached.

It was estimated that one-fourth of all white families in the entire survey received less than 400 international units of vitamin B<sub>1</sub> per adult per day. About 10 per cent selected food furnishing less than 300 units, and only half obtained the 500 unit allowance set for an adult per day. Their study was made in families of only employed wage earners, and therefore the vitamin B<sub>1</sub> values received by the families where there was unemployment or relief is left to conjecture.

We have been able to find only one reference in the literature to an analysis of vitamin B<sub>1</sub> in the diets of pregnant women. McCance, Widdowson and Vernon-Roe,<sup>17</sup> in a study in England found that the vitamin B<sub>1</sub> value of the diets advanced as food expenditures rose. Only the maximum intakes of the three highest income groups studied revealed over 500 international units, while the minimum intake for all groups fell below 300 international units.



NOTE—ADAPTED FROM STIEBELING & PHIPARD

Fig. 1.

We may examine the recent report of Jolliffe<sup>18</sup> who agrees with Strauss<sup>19</sup> that beriberi is endemic in this country. Jolliffe regards the present daily American dietary as containing from 300 to 450 international units of vitamin B<sub>1</sub>, and discusses the faults of a national diet which results in an annual per capita consumption of 100 pounds of sugar and white flour made from 4 bushels of wheat. These two sources, which furnish 55 per cent of the daily average of 2,500 calories, do not contain more than 50 international units of vitamin B<sub>1</sub>.

The safety margin above a beriberi level of Sherman's average American diet according to Jolliffe<sup>18</sup> is only 20 per cent by the Cowgill ratio. Jolliffe's analysis of diets in 1,394 North American families by the same means shows interesting results. According to certain levels of food expenditure the safety factor ranged from 3 to 25 per cent. It is apparent that the entrance of a single disturbing factor may obliterate this scant margin of safety and bring on the clinical symptoms of a deficiency. In this light, Jolliffe regards gestational neuritis as a misnamed appearance of beriberi.

Beriberi, endemic in the Orient, has afforded an opportunity to witness the interrelationship of severe degrees of vitamin B<sub>1</sub> deficiency and pregnancy.

Boerma,<sup>20</sup> whose observations were made in Java, believes that beriberi, appearing during pregnancy, is conditioned by the vomiting, and is more severe if a serious illness has preceded the pregnancy. While the evolution of the pregnancy is not hindered by the beriberi, it is his view that the greatest danger to the woman came from a cardiac insufficiency during delivery. Balfour and Tolpade, quoted by Guggisberg,<sup>21</sup> state that every pregnant woman in South India suffers from beriberi. The extremely high maternal mortality in these women is caused by a macrocytic type of anemia which is quickly improved by yeast, liver extract, and a meat diet, all of which are rich in the vitamin B complex.

From Japan, Fujita<sup>22</sup> reported 39 cases of pregnancy and beriberi under his care, the beriberi appearing late in pregnancy or in the puerperium, and more frequently in summer or autumn. The regional mortality of the combined conditions ranges from 9 to 15 per cent, and although only one mother in Fujita's series died, approximately 25 per cent of the babies were lost. In the Philippine Islands, a high neonatal mortality rate has been ascribed by Andrews<sup>23</sup> to an infantile beriberi due to a deficiency of the growth and nerve development factors of the mother's milk.

One of the notable clinical manifestations of a deficiency in vitamin B<sub>1</sub> is the polyneuritis of pregnancy, which sometimes accompanies severe hyperemesis gravidarum.

Luikart,<sup>24</sup> Plass and Mengert,<sup>25</sup> and Strauss and McDonald<sup>26</sup> have ably demonstrated this relationship and the therapeutic effectiveness of vitamin B<sub>1</sub>. With the synthesis of thiamin the more advantageous parenteral route of administration has been made possible. Here the therapeutic dose depends upon the clinical reaction to measured amounts of the remedy.

In one instance Hildebrandt and Otto<sup>27</sup> gave 1,782 mg. of vitamin B<sub>1</sub> during a pregnancy complicated by a severe polyneuritis. There was no toxic reaction to the drug, and no excretion of the vitamin in the urine up to the time of delivery. Evidently the demand did not permit saturation even with so large an intake.

On the other hand deleterious effects on reproduction of very large doses of vitamin B<sub>1</sub> may be possible.

Sure<sup>28</sup> demonstrated that in rats fed 100 micrograms of thiamin daily, sterility occurred in the females of the second generation. Continuing this study it was found that a daily dose of 400 micrograms produced entire failure of lactation in the third generation.

Saturation tests, according to Neuweiler,<sup>29</sup> show that pregnant women tend to retain a large proportion of a parenteral dose of vitamin B<sub>1</sub>, especially if any manifestations of toxemia are present. Since it appears in certain such instances that saturation with subsequent excretion of vitamin B<sub>1</sub> in the urine may be difficult to obtain, an attempt should be made to reach an excretion-producing dosage before considering that this type of treatment has been adequately used, unless clinical improvement has appeared.

The frequent occurrence of a hypochromic macrocytic anemia in pregnant women suffering with beriberi, or a less marked vitamin B<sub>1</sub> deficiency, has pointed to a similar etiology of the two conditions. Although marked improvement has followed the use of vitamin B<sub>1</sub> containing substances in this type of anemia, it is by no means definitely proved that lack of this factor alone is the cause. According to Elsom,<sup>30</sup> the deficiency in the diets of such anemic women probably concerns the entire B complex.

Only a few complications caused by vitamin B<sub>1</sub> deficiency have been noted in connection with human parturition.

Moore and Brodie<sup>31</sup> noted abnormally profuse hemorrhage during a precipitate delivery in a woman whose diet was markedly deficient in vitamin B<sub>1</sub>. The baby died of hemorrhage and at autopsy gross and microscopic changes resembled those in experimental animals on a deficiency diet. There was no evidence of disease of the hematopoietic system.

The toxemias of late pregnancy have been ascribed to a vitamin B<sub>1</sub> deficiency.

Siddall<sup>32</sup> advances the theory, based upon his observations on prenatal cases afflicted with beriberi in China, that normal function of the pituitary gland is possible only when an adequate supply of vitamin B<sub>1</sub> is available. He believes that in the pregnant woman a deficiency leads to an over-compensation or malignant hyperfunction of the gland. This in time produces the various symptoms of toxemia; disturbed carbohydrate metabolism, edema, elevated blood pressure, nausea and vomiting, and an increase in prolactin and decrease in estrin. According to this theory an adequate and constant supply of vitamin B<sub>1</sub> should prevent toxemia and perhaps cure it. In view of the saturation excretion data already considered, it may be that the doses of synthetic vitamin B<sub>1</sub> which were used in the clinical studies based upon this hypothesis were inadequate as curative therapy. On the other hand the pituitary change may have been too well established to have been influenced rapidly.

Yasunami<sup>33</sup> in a recent contribution from Japan found in his toxemia cases, mostly from a group with low living conditions, that treatment with vitamin B<sub>1</sub> in large doses was very effective, especially, in avoiding convulsions in the pre-eclamptic patients. Ross and his co-workers<sup>34</sup> in a dietary study in North Carolina, however, failed to note a decrease in the incidence of toxemia during the latter part of pregnancy in a controlled group of patients who received an adequate amount, approximately 1,000 international units of vitamin B<sub>1</sub> in the form of yeast tablets daily.

As to the relationship between vitamin B<sub>1</sub> deficiency and the toxemias, Vignes<sup>35</sup> remarks upon the diminution in volume of the liver observed in the deficiency cases, the diminution of glycogen in this organ and the muscles, and a reduction in the tolerance of carbohydrates. The latter, not being transformed into glycogen, encumber the blood as an excess of glucose, a hyperglycemia resulting. Much has been written on the role of vitamin B<sub>1</sub> in the metabolism of carbohydrates, and not a few obstetric authors today recommend supplemental administration of vitamin B<sub>1</sub> during therapy with large or continued injections of dextrose or glucose.

The minor paresthesias and neuritides of the extremities and back complicating pregnancy and the puerperium have responded quickly in many instances to vitamin B<sub>1</sub> therapy. Stillbirths were observed in a number of cases of pregnancy complicated by nutritional deficiencies in Vignes' clinic, and he regards a vitamin B<sub>1</sub> deficiency as frequently responsible for sterility, abortion, and ineffectual labors with post-partum inertia and hemorrhage.

Subsequent to these clinical observations Ueno<sup>36</sup> has shown by animal experiments that marked changes in the reproductive cycle follow a vitamin B<sub>1</sub> deficiency diet. White rats developed a stationary sexual stage, and even matings with normally fed rats failed in high percentage. The development of fetuses in the successful matings was hindered, and abortion and resorption were frequent. Fetuses born alive were small and weak. Labors were characterized by

inertia and subinvolution. The same effects were seen by Moore and Brodie,<sup>31</sup> who noted, in addition, that deaths during the nursing period were caused by hemorrhages, while myelin degeneration of the vagus and phrenic nerves was present. Before death such young rats exhibited signs of advanced beriberi. Commenting on his own animal work and its relation to the human organism, Shin<sup>37</sup> describes an infant which exhibited classical signs of beriberi when only two days old. He states that at times the newborn infant may show evidence of the disease before the mother, on a vitamin B<sub>1</sub> deficient diet, had developed the puerperal lesions so frequently seen in his district in China.

The metabolism of vitamin B<sub>1</sub> in relation to the human reproductive cycle has been studied only recently. The function of the placenta as a place of storage has been questioned.

Stahler<sup>38</sup> believes that the placenta is permeable to this vitamin since the blood of infants showed a concentration similar to that of the mother, even though the latter had been given intramuscular injections of vitamin B<sub>1</sub> just before labor. Guggisberg<sup>21</sup> also regards the placenta as a filter which permits the demands of the fetus to be adequately withdrawn. He remarks that vitamin B<sub>1</sub> distinguishes itself as an element of low storage capacity and that, without marked reserves in other parts of the body, the placenta finds no sufficient reserve stores to seize and place at the disposal of the fetus. Stahler also showed that the expressed extract of the placenta contained less vitamin B<sub>1</sub> proportionately than the fetal blood.

Dubrausky and Lajos,<sup>39</sup> however, believe that the placenta is a reservoir and plays an active part in supplying the fetus. They found that the vitamin B<sub>1</sub> content of the placenta fluctuated between 108 micrograms per cent and 980 micrograms per cent. Since this was greater than the value of either the maternal or fetal blood, as they determined them, it might seem that their conclusion was well supported.

The requirement of this vitamin for the human being has been a matter of considerable discussion. The experiments of Osborne and Mendel years ago indicated that there was a greater need as the size of the body increased. In recent years a relationship of the vitamin B<sub>1</sub> requirement to the caloric intake has been recognized.

Cowgill,<sup>40</sup> by determining the minimum vitamin B<sub>1</sub> requirement of the mouse, rat, dog, and pigeon, found that he could express the minimum requirement in terms of units of body weight and metabolism. His formula for the human being may be expressed as follows:

$$\frac{\text{Vitamin (daily requirement of vitamin B}_1\text{)}}{\text{Calories (daily total energy exchange)}} = K (\text{weight in kilograms}) \times 0.0284.$$

The result was expressed in milligram equivalents of his standard test powder. Since the adoption of the Standard International Unit in 1938 as the potency of 3 micrograms of thiamin chloride, the weight in kilograms must be multiplied by a human species constant of 0.00426 to obtain the requirement in the present international unit. It should be understood that such needs represent only the minimum or beriberi preventing level.

Cowgill states that, in view of the relationship of the vitamin B<sub>1</sub> requirement to the caloric intake, a simple form of standard to express the vitamin B<sub>1</sub> need is the number of units per hundred calories. Stated in this manner his minimums are approximately 10 international units per 100 calories for a normal human adult. Rose<sup>41</sup> recommended 15 international units per 100 calories, and Daniel and Munsell<sup>42</sup> point out that this would mean roughly 250 to 400 international units

per day for an adult. According to Cowgill<sup>43</sup> it appears that adults require a daily minimum approximately 300 to 350 international units of the vitamin, which is equivalent to about 1 mg. of thiamin. Vorhaus, Williams, and Waterman<sup>44</sup> have calculated the same amount as the vitamin B<sub>1</sub> requirement of the normal adult. Stiebeling and Phipard in a survey of diets in the United States set 500 international units as the daily allowance of "per requirement units," for an adult of twenty years or more. Recently, Williams and Spies,<sup>1</sup> in discussing the vitamin B<sub>1</sub> sparing action of fat, prefer to use the ratio T(thiamin)/non-fat calories, to determine the margin of protection against beriberi in various diets.

The majority of workers in the field of nutrition agree that the requirements for pregnancy are decidedly higher than for a nonpregnant individual. Vignes is of the opinion that the increased requirement of the pregnant woman is conditioned principally by demands of the fetus.

In pregnancy many of the factors regarded as ordinarily increasing the requirement are present: growth of the fetus, reserve growth, increase in metabolism (the increase in the basal metabolic rate may be attributed largely to fetal metabolism), increased urinary excretion, interference with proper alimentation, in early pregnancy due to the vomiting and in late pregnancy due to displacement of the gastrointestinal tract. There are, of course, the ever present factors of economy, ignorance, and misguidance in selection of food.

The Health Committee of the League of Nations<sup>45</sup> proposed in their nutritive requirements for pregnancy that 150 to 250 international units of vitamin B<sub>1</sub> are essential. Cowgill<sup>46</sup> regards these requirements as inadequate. He suggests a daily intake for the American mother of not less than 15 and preferably as high as 20 international units per 100 calories, for a 2,500 caloric intake, 375 to 500 international units. Dieckmann<sup>47</sup> sets 400 international units for the first twenty-eight weeks, then 600 international units to term. Rose believes that pregnant women should have double the quantity of vitamin B<sub>1</sub> required by the normal adult. Baker and Wright<sup>48</sup> recommended an intake during pregnancy of three to five times the requirement of the nonpregnant state.

In a series of pregnant women studied in Holland, Westenbrink and Goudsmit<sup>49</sup> found a lowered excretion of vitamin B<sub>1</sub>, even when there was a supplemental intake, as compared with nonpregnant women on the same diet. With few exceptions there was no evidence that the pregnant women were saturated with vitamin B<sub>1</sub>. Such work on saturation and urinary excretion tests appear to support the ideas regarding increased requirements of vitamin B<sub>1</sub> during pregnancy and its complications. Gaetgens<sup>50</sup> believes pregnancy does not increase the vitamin B<sub>1</sub> need. He states that the average of 1 mg. of aneurin (thiamin) which is required for a normal male adult should be sufficient for a pregnant woman.

In the course of a nutrition survey begun in Philadelphia last year, using over 500 pregnant women in various prenatal clinics as subjects, a study of vitamin B<sub>1</sub> in the diets of certain of these women developed as an interesting outgrowth. We decided to estimate the dietary intake of vitamin B<sub>1</sub> and correlate it with electrocardiographic findings as well as with clinical deficiency symptoms and some obstetric factors. Ninety-one patients attending the prenatal clinic of the Presbyterian Hospital were studied, and there was no special selection on the basis of stage of pregnancy or degree of parity. A nutritionist interviewed each woman and instructed her in the proper method of recording food intake over



a period of seven days. There was a second interview during which the food record\* was scrutinized and checked and the patient was scheduled for an electrocardiogram. We feel that the food records, obtained in the manner described, furnish a reasonably good picture of the usual diets of these pregnant women. An estimate of the food value was made from these records and the vitamin B<sub>1</sub> values were recorded in terms of international units, in most instances as set forth in *Food Values of Portions Commonly Served*, Second Edition, 1940, prepared by Bowes and Church.<sup>51</sup>

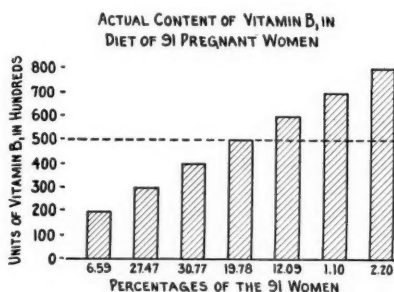


Fig. 2.

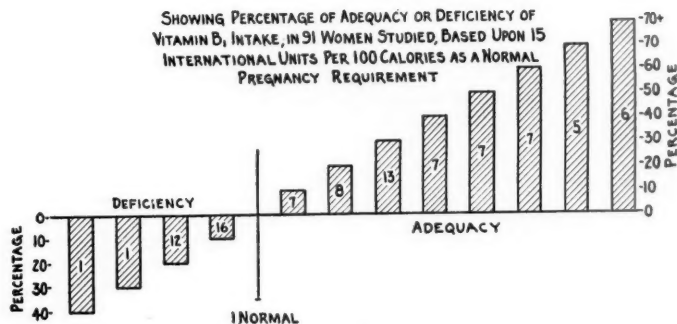


Fig. 3.

The vitamin B<sub>1</sub> values were computed for a great many foods on the basis of the fresh, raw state, depending upon the availability of the data. No attempt was made to determine cooking losses, since these vary with the method followed. When wide ranges in vitamin B<sub>1</sub> value were reported, the lowest value was chosen arbitrarily, since we did not know which value represented the greater number of assays.

The vitamin B<sub>1</sub> values of these diets have been arranged graphically to show the actual content in hundreds of international units. This chart shows the percentages of vitamin B<sub>1</sub> values in relation to the suggested daily requirements of 500 international units for a normal adult set by Stiebeling and Phipard.<sup>16</sup> It serves to indicate how deficient the diets of these women must be when it is generally agreed that the requirements are higher during pregnancy and lactation (Fig. 2).

\*The forms used for the food analyses were patterned after those designed for teaching purposes at the Dental School of the University of Pennsylvania.

It is recognized that the need for vitamin B<sub>1</sub> depends upon the caloric intake, and Cowgill states that a pregnant woman requires 15 international units per 100 calories. Applying this ratio, we have found the relationship of the requirement to the actual intake of vitamin B<sub>1</sub> expressed in Fig. 3. Practically one-third of the group was not receiving an adequate amount of vitamin B<sub>1</sub>.

Considering moderate to marked nausea and vomiting as a vitamin B<sub>1</sub> deficiency symptom, 30 per cent of the patients showing inadequate intake exhibited this symptom as contrasted with 10 per cent of the

COWGILL PREDICTION CHART  
(EACH DOT DENOTES AN INDIVIDUAL)  
MINIMUM OR BERIBERI PREVENTING LEVEL

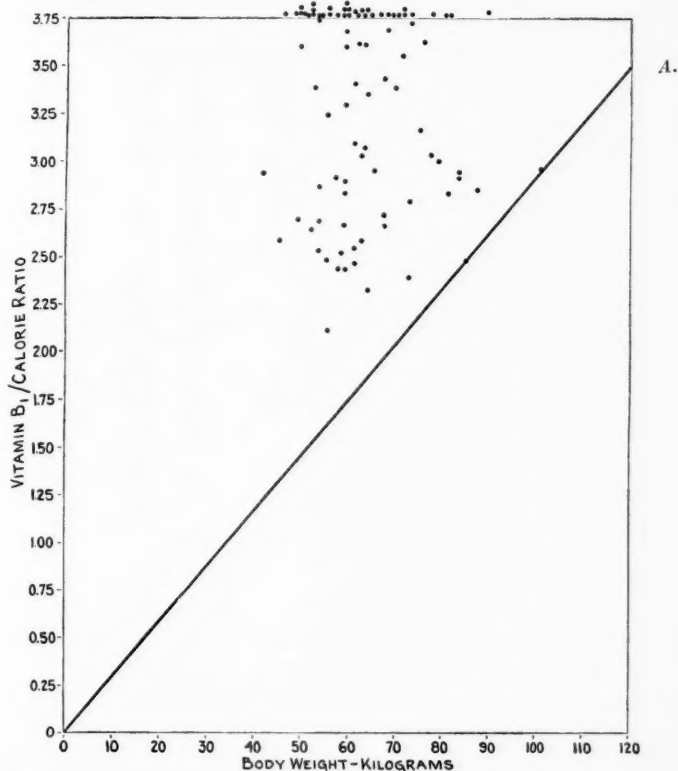


Fig. 4.

patients who had sufficient. Practically, a similar distribution of other vitamin B<sub>1</sub> deficiency symptoms, as fatigue, paresthesias, cramps, and dyspnea, was found. The clinical data were secured from histories recorded by disinterested persons, and, therefore, the information obtained from patients was unbiased. Still, we feel that in a relatively small series, no definite conclusions should be drawn concerning such deficiency symptoms.

A third calculation has been made possible by the use of the Cowgill prediction chart (Fig. 4). By an analysis of diets known to be asso-

ciated or not with beriberi, he has determined a relationship between the vitamin B<sub>1</sub>/caloric ratio and the body weight. On such a chart we have set out the individual instances of our study group. The line AO repre-

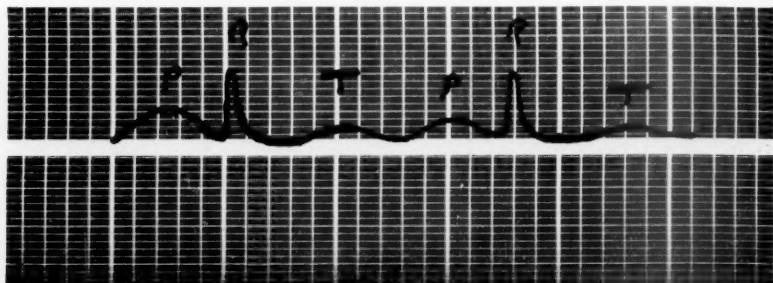


Fig. 5.—Electrocardiographic abnormalities in vitamin B deficiency. P-wave normal, QRS slurred in the descending limb of R. T-wave rises slowly and is flattened.



Fig. 6.—Typical tracing showing vitamin B<sub>1</sub> deficiency.

sents the beriberi, preventing level of the diets studied by Cowgill. The chart represents the vitamin B<sub>1</sub>/caloric ratio of the diets plotted against the weight in kilograms.

The margin of safety of a diet against beriberi is, of course, the percentage of the vitamin B<sub>1</sub>/caloric ratio above the minimum level for a particular weight. This has been computed for each one of the group,

and the range was found to extend from 0 to 180 per cent. The percentages of the margin of safety have been plotted out in Fig. 7. It will be seen that about one-fourth have under a 50 per cent, and two-thirds under a 100 per cent margin of safety.

When the histories of the 9 women with the lowest margins of safety were reviewed, it was found that 5 had had marked to excessive nausea and vomiting of pregnancy, and in addition 1 had had mild neuritis.

After analyzing our food records, we began a correlation between any possible cardiac lesions as revealed by the electrocardiograph, and the actual content of vitamin B<sub>1</sub> in the diets.

Electrocardiographic studies in the vitamin B<sub>1</sub> deficient hearts have been characteristic in that the rate is usually slow and the voltage low. There is a slight slurring of the descending limb of the R-wave, a slowly rising, round T-wave, and a prolongation of the P-Q interval. A diagrammatic drawing of a typical vitamin deficient QRS and T-wave is

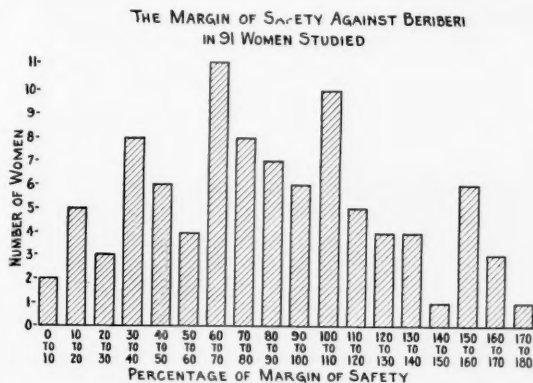


Fig. 7.

shown in Fig. 5. Weiss and Wilkins,<sup>52</sup> in their work on the "nature of cardiovascular disturbances in nutritional deficiency states," have demonstrated similar electrocardiographic changes in a study of vitamin deficient rats.

Of the 91 electrocardiograms studied, 8 showed characteristic changes mentioned above. In no one of these was there any history or physical signs relating to previous cardiac disease. A typical tracing showing vitamin B<sub>1</sub> deficiency is illustrated in Fig. 6. When we reviewed the vitamin content of the diets of these 8 women at the time the electrocardiogram was made, we found that, according to the ratio of 15 international units to 100 calories, 4 were deficient, and 4 had an adequate amount of vitamin B<sub>1</sub> in the diet. One case, however, had only a plus 2 per cent adequacy. In this connection Weiss remarks that he has observed patients with histories of vitamin B<sub>1</sub> deficiency in whom the only detectable objective change was in the electrocardiogram.

There was no correlation observed between the significant electrocardiograms and various other deficiency symptoms. According to the

Cowgill prediction chart (Fig. 4), 7 of these 8 women had a margin of safety of less than 100 per cent above the beriberi level. The lowest margin of safety was 54 per cent and the highest 143 per cent.

#### SUMMARY AND CONCLUSIONS

Vitamin B<sub>1</sub> or its synthetic equivalent, thiamin chloride, has been shown to be a dietary factor essential to the normal human adult.

The literature indicates that the requirement for this vitamin is definitely increased in pregnancy.

The effects of an outstanding deficiency, beriberi, on pregnancy have long been recognized in the Orient, yet many subclinical deficiencies in this part of the world have been mislabeled as direct results of the gestation itself.

Many workers in the fields of nutrition have shown that the average American diet provides an insufficient margin of safety against beriberi prevention.

An index of the need for and of the metabolism of thiamin chloride by saturation excretion experiments has been recently established.

Not only have the toxemias of late pregnancy been explained on a theoretical basis of vitamin B<sub>1</sub> deficiency, but, practically, in the Orient they have been shown to be amenable to vitamin B<sub>1</sub> therapy.

Animal experimentation has demonstrated the inimical effect of a vitamin B<sub>1</sub> deficiency upon the reproductive cycle.

Evidence has accumulated to show that the placenta acts only as a filter in the maternal fetal transference of this substance.

Our studies of the food records showed that one-third of a group of 91 pregnant women were not receiving an adequate amount of vitamin B<sub>1</sub>, calculated on a ratio of 15 international units per 100 calories.

Practically two-thirds of this group were receiving less than 500 units of vitamin B<sub>1</sub>, the standard followed by Stiebeling and Phipard.

There was some positive correlation between the inadequacy of the intake and deficiency symptoms, such as excessive nausea and vomiting, fatigue and paresthesias.

The margin of safety above a beriberi level as calculated on a Cowgill prediction chart ranged from 0 to 180 per cent. One-fourth had a margin of safety under 50 per cent, and two-thirds presented one under 100 per cent.

The electrocardiograms of 8 women in the group showed changes signifying a vitamin B<sub>1</sub> deficiency. There was no positive correlation between these electrocardiograms and the adequacy of the vitamin B<sub>1</sub> intake.

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**Sezary, A.: The Local Treatment of Soft Chancre and Cutaneous Pyoderma by Sulfamide Powder, Presse Méd. 47: 1408, 1939.**

The author quotes Lepinay's experience in the treatment of soft chancre and various pyodermas by the local application of the new para-amino-phenyl-sulfamide. Lepinay, treating 11 cases by dusting the powder upon soft chancres, obtained 10 cures. The one not responding appeared to be a case of mixed chancre. At the end of twenty-four hours, suppuration decreases considerably and may disappear, pain leaves, and the ulceration is halted. The second day the scarring begins. Healing is complete by the third to the eighth day.

The treatment is well tolerated. If the sulfamide powder is mixed with iodoform powder, it seems to give a double advantage, rapid healing ability with an absence of odor. With associated adenitis, Lepinay recommends sulfamide by mouth and vaccine therapy. If the lesions are old, the author recommends débridement to permit a local contact with the sulfamide powder. For those lesions involving the anus, sulfamide suppositories may be used.

Encouraged by his results from treating soft chancre with sulfamide, he used it also in several cases of pyoderma and cutaneous gangrene. He obtained rapid healing, followed by epidermatization, in these cases.

CLAIR E. FOLSOME.

## ABDOMINAL PREGNANCY\*

CLIFFORD B. LULL, M.D., PHILADELPHIA, PA.

**I**MPREGNATION of the human ovum does not always result in an intrauterine gestation. I wish to limit my discussion to those tragic cases where the impregnated ovum, either through the process of tubal abortion or rupture, attaches itself and continues to grow in the peritoneal cavity, this viewpoint being taken because of the improbability of the occurrence of primary abdominal pregnancy. I should also like to confine my discussion to those cases which develop in the abdominal cavity as a secondary pregnancy beyond the sixth month, up to and approaching full term. This discussion will pertain chiefly to the management of this unusual complication of pregnancy and include brief case reports of 5 patients whom I have had the opportunity of observing and operating upon during the past twenty years.

According to Bland and Montgomery, between 1813 and 1938, a total of 321 approximately full-term or at least viable secondary abdominal pregnancies were reported. Taking into consideration the number which undoubtedly have not been reported, this condition still remains one of the most uncommon complications of obstetric practice. It is generally conceded that the maternal mortality rate associated with this condition is between 30 and 40 per cent, with a fetal mortality rate of approximately 50 per cent. Even though the child does survive, Nature has done all within its power to destroy it by causing many deformities and abnormalities that make development of a normal human being practically impossible. On the other hand, a sufficient number of cases have been reported where the offspring has been normal, that should one encounter a patient where delay in operation might mean a viable child, it would seem advisable to defer the operation.

According to Bodenheimer, it is not always possible to make this very difficult diagnosis previous to operation. In a series of 236 cases that he studied, only 83 were diagnosed preoperatively.

Eminent medical authorities of this country agree that the management of the placenta is the most important phase of this condition. Practically all standard textbooks and other literature on the subject advise leaving a live placenta in situ unless it can be removed very easily. Schumann in his very excellent monograph on ectopic pregnancy, published in 1928, states that the placenta should be left in situ and if necessary, subsequently removed. He refers to Jewett's case, published in 1923, where the placenta was very large and firmly attached to the right side of the posterior surface of the uterus; the right broad ligament extending into the cul-de-sac and up the posterior pelvic wall as far as the brim of the pelvis, overlying the iliac vessels on that side. In this case the placenta was left in situ, the cord ligated and cut close to its insertion, and the patient made an uneventful recovery. He also states: "The tendency is steadily growing to regard the placenta as a digestible, autogenous tissue mass and to leave it undisturbed; the child and membranes, as well as any pathological pelvic organs being removed and the abdomen closed without drainage." In his recent textbook on obstetrics, he says that reports of recovery without difficulty make this procedure the best plan of treatment, but makes no statement as to the possibility of

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failure of absorption. Bland and Montgomery also advise this procedure but make the statement that the placenta may have to be removed at a later date.

It has been fairly well demonstrated, in the number of reported cases, that when this procedure of leaving the placenta in situ is carried out, recovery usually is rapid and uneventful. The older plan of marsupialization with moderate packing of the cavity with gauze has been frowned upon by many writers because of the prolonged convalescence and the possibility of sinus formation which might necessitate secondary operation for repair of the abdominal wall. Objection has been raised to leaving the placenta in situ and closing the abdomen without drainage because of the possible detachment with subsequent hemorrhage following operation. This, however, does not seem to occur. This procedure is followed in those cases where the placenta is still alive. When operating upon a patient where the fetus has been dead for some time, there is usually no difficulty in removing most of the placenta and the membranes along with the fetus. This, however, is not constant, as in one of the cases I am reporting, although the fetus had been dead for some time the placenta was still highly vascular and as a result profuse hemorrhage occurred. Recently Nicodemus observed a patient in whom the placenta did not absorb, necessitating drainage of the resultant abscess and removal of the remaining portion of the placenta. And still more recently I have encountered a case in which a second operation for removal of the placenta became necessary. Because of Nicodemus' report and the one I am now making, it seems necessary to call attention to the fact that absorption does not always take place. In the case reported by Nicodemus, the diagnosis was not made prior to operation, and there had been ineffectual attempts at induction of labor from below before the abdomen was opened. The inability to induce labor and a progressive pre-eclamptic toxemia were responsible for the decision to deliver by abdominal section. A live child was obtained. The patient returned to the hospital in two months with elevation of temperature, leucocytosis, and other signs of infection. Secondary operation for drainage of the resultant abscess formation resulted in the ultimate recovery of the patient. Nicodemus stated in his case report that a search of the literature failed to reveal a similar case in the last decade.

As this feature of the management of this complication is not stressed, it seems feasible to review the management of this condition. Furthermore, any condition which has a maternal mortality rate of from 30 to 40 per cent should be considered a possible virgin field for improvement of our already supposedly too high maternal mortality. Although the subject is discussed satisfactorily in the more recent textbooks, it has occurred to me that information necessary for the guidance of the occasional operator, or one who has not encountered this complication previously, could be clarified.

It is not my purpose to formulate any strict rules to govern the management of secondary abdominal pregnancy, but rather to mention a few safeguards which might lead to a decrease in our mortality rate. Nor is it my desire to criticize what is written in the more recent textbooks but rather to elaborate upon what has already been said.

I believe the following five case reports clearly illustrate the various complications which might be associated with this condition. The first four will be discussed very briefly and the fifth in more detail because of its rather unusual outcome.

CASE 1.—The patient was a para iv in whom the diagnosis of abdominal pregnancy was made in the seventh month of gestation. It was doubtful whether the child was alive. At operation it was found to be alive but did not survive. In extracting the fetus, part of the placental attachment was torn, and a profuse hemorrhage was controlled only by packing. The patient died three hours following operation from shock.

CASE 2.—The patient was a para iii. Diagnosis of abdominal pregnancy was made at six and one-half months and a live fetus was removed which did not survive. An attempt was made to remove the placenta but the resultant hemorrhage, which was controlled only by firmly packing the placental site, made this impossible. The patient reacted nicely from the operation. On the sixth and seventh days, the packing was gently loosened and on the eighth day it was removed without any apparent difficulty. A small pack was re-inserted and at the time this was removed there was no bleeding. One hour later, however, a severe secondary hemorrhage occurred which resulted in death before combative measures could be instituted.

CASE 3.—The patient, a para vii, was admitted to the hospital at the third month of gestation with a diagnosis of threatened abortion. There had been moderate bleeding and occasional cramplike pains in the lower abdomen. Bleeding ceased after rest in bed and sedation, and she was discharged from the hospital without a vaginal examination. This patient was not seen again until she was approximately six and one-half months pregnant, when she was admitted because of rather acute abdominal distress with slight bloody vaginal discharge. At that time, examination revealed the presence of a fetal head in the cul-de-sac and a uterus, the size of which was not commensurate with the estimated month of gestation. These findings were corroborated by x-ray which revealed the presence of two fetal skeletons. The patient stated she had not felt life for several weeks. Immediate operation was performed and the placenta was found lying on top of the uterus and coils of intestine. Both fetuses were behind the uterus and underneath the placenta. In order to remove them, some of the placental attachment had to be freed. Although life had not been felt by the patient for several weeks, profuse hemorrhage occurred when the placenta was detached. The fetuses were removed as quickly as possible and packing was inserted. The patient was returned to the ward in good condition and the packing was not disturbed for ten days, at the end of which time the patient was prepared as for any abdominal operation, taken to the operation room, and after the usual preparation, the packing was carefully and slowly removed. The patient was kept in the operating room for two hours following this procedure, and my assistants and I remained scrubbed. There was no secondary hemorrhage. A shorter pack was inserted and the patient was returned to the ward. The second pack was removed on the fourth day without serious bleeding. The resultant sinus drained for about three weeks and then closed spontaneously. Examination of this patient two years later showed her to be in good condition with no palpable pelvic mass.

CASE 4.—The patient, a nullipara, was seen in consultation in an up-state town when she was supposedly seven and one-half months pregnant. The diagnosis of abdominal pregnancy had been made by the family physician and fetal motion had ceased four weeks previously. The patient had been running a temperature of 101° F., in the evening, for two weeks before being seen by me. Because of probable post-operative complications, she was removed to Philadelphia by ambulance. After careful preparation, including blood typing, she was operated upon. Upon opening the peritoneal cavity a macerated fetus was found enclosed in a sac which had a very dirty, greenish yellowish appearance. There was no evidence of a placenta.

The sac seemed to be entirely walled off from the rest of the peritoneal cavity, and as the incision was made directly over the sac, none of the other abdominal viscera were seen. The macerated fetus was removed, but because of evident infection no attempt was made to remove the sac, which was marsupialized and drained. The drainage was very markedly purulent. No bleeding occurred, and the patient, after draining rather profusely for two or three weeks, made an uneventful recovery. Unfortunately, this patient died four months following operation of miliary tuberculosis, but up to that time she had had no abdominal symptoms.

CASE 5.—The patient, a para ii, 38 years of age, who had not been pregnant for nineteen years, was admitted to my service at the Philadelphia Lying-in Hospital on Jan. 1, 1940, with Jan. 26, 1940 as the expected date of confinement. Her family physician informed us that he had been in attendance on her for forty-eight hours prior to admission, during which time she had been in more or less constant labor, but according to his findings, had made no progress. On abdominal examination the child could be felt very distinctly and the heart sounds were auscultated in the lower left quadrant. A large, doughy mass could be palpated on the right side, but the fundus of the uterus could not be felt. Vaginal examination revealed the fetal skull to be in the left vaginal vault. The sutures and fontanels were easily outlined. The cervix was displaced to the lower right angle of the vagina, was soft, but not effaced nor dilated. On bimanual examination the uterine contour could not be outlined. A diagnosis was made of spurious labor and an abdominal pregnancy with a living child. As the patient had not been under our supervision and because she had had no rest for forty-eight hours, immediate operation was deemed inadvisable. This in spite of the fact that the usual history of these patients is that following attempts at labor the fetus usually dies. She was given morphine which enabled her to get much needed rest. In the meantime, routine studies were carried out. X-ray did not corroborate our diagnosis. The blood Wassermann was found to be positive, while other studies were essentially negative. In view of the fact that the child was living and the patient's general condition much improved, decision to operate was made on January 6. Before proceeding, however, the patient was typed and the necessary blood was obtained and in readiness in the operating room. The fetus seemed to be lying entirely on the left side, and because of our experience in previous cases, the abdomen was opened through a left rectus incision. Upon opening the peritoneum about 30 c.c. of blood and clots was found in the peritoneal cavity. There was no evidence of an amniotic sac. The fetus was lying on top of the intestines. A female child, weighing 4 pounds 13¾ ounces, was removed; she appeared to be in good condition and cried immediately. The placental site was then very carefully and gently inspected in order to avoid hemorrhage. It was found that the placenta was attached, starting at the right cornu of the uterus and extending upward on the right side to about the level of the umbilicus. It was not only attached to the lateral pelvic wall but the intestines were also involved. The cord was then ligated and cut close to its placental attachment. The loss of blood was minimal and the abdomen was closed without drainage. Patient's convalescence was uneventful. The highest elevation of temperature occurred on the second day postoperatively when it reached 100° F. The patient was kept in the hospital three and one-half weeks, during which time she had no unusual symptoms. At the time of discharge from the hospital there was a distinct fullness in the lower right part of the abdomen and a mass about the size of a small grapefruit could be palpated. This patient insisted upon going home and as her temperature was normal and she had no complaints, she was permitted to do so. Three weeks later she returned complaining of abdominal pain, particularly in the right side of the abdomen, associated with nausea and vomiting and more or less obstinate constipation. She had had some vaginal bleeding and one attack of persistent vomiting. At this time there was a large, well-defined mass in the lower abdomen, approximately the size of a four months' gestation. She was readmitted and kept under observation. Her Friedman test was returned positive, but a second Friedman done in dilution proved to be



negative. Within a week the mass had increased a trifle in size and she had experienced two other attacks of nausea and vomiting together with difficulty in proper elimination. She was afebrile, had a normal sedimentation rate, and normal leucocyte count. Because of the increase in size of the mass and because of questionable partial intestinal obstruction, it was decided to reopen the abdomen. This was done on March 6, two months after the original operation. The abdomen was opened through the old incision, and upon incising the peritoneum a large mass was found originating in the right side, looking not unlike an ovarian cyst. It was completely encapsulated and was adherent on all surfaces. Adhesions to the parietal peritoneum were freed without difficulty and gave rise to no bleeding. On continuing to break up the adhesions it was found that posteriorly several sections of intestines and the posterior peritoneum were so firmly united with the sac that to continue attempting this procedure would have resulted in disaster. By this time, however, the encysted mass could be brought well up into the abdominal incision. It was incised and a large basinful of necrotic placental tissue weighing 660 Gm., together with organized blood clot, was removed. There was no fresh bleeding. Evidently the increase in size had been due to hemorrhage into the cyst cavity. Microscopic examination of the tissue removed proved it to be definitely placental tissue. The sac was then cut off down to the portion where it was densely adherent and the edges sewed to the parietal peritoneum. A small pack was inserted into the cyst cavity and the usual closure of the abdomen completed the operation. The patient reacted very well. Starting on the third day, a small amount of packing was removed each day until it was entirely out on the seventh day. Her convalescence was uneventful and she was discharged from the hospital on the fourteenth day in good condition with the wound entirely healed. The discharge from the sac cavity at no time was purulent in character. Up to the present time the patient has continued to be in good health and the baby now weighs over 7 pounds.

In reviewing these summaries I would like to point out some pertinent facts as to the good or bad judgment exercised in the management of these five cases.

In the first case, the removal of the child was not accomplished with sufficient care so as not to disturb the placenta, and fatal hemorrhage resulted. Also, prompt combative measures were not in readiness to control shock from hemorrhage.

In the second case, the hemorrhage was unavoidable, but sufficient safeguards were not on hand at the time of removal of the packing.

In the third case, unavoidable hemorrhage occurred but proper blood transfusion and care at the time of operation, together with proper safeguards at the time of removal of the packing, resulted in recovery of the patient.

In the fourth case, where the child was known to be dead, all precautions were taken at the time of operation and fortunately no hemorrhage was encountered. No effort was made to remove the sac, because it was thought to be walled off from the other viscera and was potentially infected. I believe that an attempt to do so would have resulted in peritonitis.

The successful outcome of the fifth case, was due to the careful study of the patient's general condition, proper blood typing prior to operation, good judgment in deciding when to operate and where to make the incision so as to avoid the placenta, and the great care exercised in inspecting the placental site. At the second operation, I believe the

incision and removal of the encysted placenta without attempting to remove the entire sac, had a definite bearing on the patient's ultimate recovery.

From my experience in observing these five cases, together with what I can gather from the most modern textbooks and recent literature on the subject, I would like to offer the following conclusions:

*First*, In the management of advanced ectopic pregnancy or so-called secondary abdominal pregnancy, there can be no absolute rule as to procedure. However, certain general principles should be followed. In other words, each patient must be individualized.

*Second*, The advisability of delaying operation with the idea of obtaining a living child is questionable, inasmuch as many of these children have congenital abnormalities and the risk to the mother in deferring operation seems to be greatly increased. When the diagnosis is made late in pregnancy, waiting a week or two seems advisable but operation should be performed between the thirty-sixth and the thirty-eighth weeks. Permitting the patient to advance to full term increases the maternal risk and decreases the chances of having a living offspring.

*Third*, If death of the fetus occurs, it seems advisable to defer operation for three or four weeks until the vascularity of the placenta has been markedly decreased and a partial separation has taken place. During the waiting period the patient should be kept in the hospital under close observation for hemorrhage and infection of the gestational sac. If the fetus has been known to be dead for several weeks, immediate operation is indicated.

*Fourth*, Careful preparation for combating possible hemorrhage should be made before operation is attempted. The patient's blood should be typed and the necessary blood at hand, so that, if necessary, it can be given immediately.

*Fifth*, Incision of the abdominal wall should be made over the site of the child rather than over the placenta. This of course is not always possible, but as demonstrated in Case 5, can sometimes be done.

*Sixth*, Careful removal of the child without disturbing the placental site is important. This is not always possible, however, as demonstrated in Case 3. When it is seen that the placenta will be partially detached in removing the fetus, the larger vessels should be ligated before attempt at separation is made.

*Seventh*, When operating upon a patient where the fetus has been known to be dead for some time, the fact that removal of the placenta may still give rise to serious hemorrhage must not be lost sight of, and although removal can usually be accomplished, it is necessary in some instances to resort to packing to control the bleeding. It seems advisable not to disturb the packing for at least ten days.

*Eighth*, In operating upon a patient where the fetus has been dead for some time and there is evidence of infection, approach to the sac should be made with care and if possible, extraperitoneally. These cases should always be drained and removal of the sac should never be attempted.

*Ninth*, When hemorrhage is encountered and packing is necessary, removal of this packing, after it has been loosened on several successive days, should be attempted only after careful preparation has been made for further transfusion and reopening of the abdomen.

*Tenth*, Where the placenta is alive and a living child removed, no attempt at separation or removal of the placenta should be made. The abdomen should be closed without drainage.

*Eleventh*, In view of our recent experience, the placenta does not always resorb and as in Nicodemus' case, may even result in abscess formation. When the former occurs, removal of the placenta should be deferred for two months, unless there is evidence of abscess formation, or as Adair points out, intestinal obstruction, at which time immediate operation is indicated. If secondary removal becomes necessary and the entire sac wall cannot be removed, marsupialization with packing of the cavity seems to be indicated.

In drawing up the aforementioned conclusions, I have endeavored to show the dilemmas into which we were placed in managing these five cases and trust that I have adequately stressed the importance of properly safeguarding the patient against tragic complications by making a proper diagnosis, fortifying the patient against shock, operating at the proper time, and in the proper surroundings where adequate equipment and medication are available to combat shock, if it should occur; and last, but not least, using proper judgment and technique with regard to the placenta.

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#### DISCUSSION

DR. CARL H. DAVIS.—Last year a colored girl, on my service at Delaware Hospital had a secondary abdominal pregnancy that followed rupture of the right tube. The technique described by Dr. Lull was followed, namely, that of removing the macerated fetus and not attempting to remove the placenta. The patient made an uneventful recovery and has had no trouble since then.

One point in treatment should be emphasized, and that is the necessity of having blood available for these patients and for all patients who are admitted to a hospital with bleeding during pregnancy. Each year many women lose their lives because an effort has not been made to secure immediate typing of blood and prompt transfusion when it is needed.

DR. WILHELM LATZKO.—Dr. Lull remarked that the great majority of abdominal pregnancies are based upon the secondary implantation of an ovum separated from its original attachment in the genitals by rupture or expulsion. This widespread conception assumes that the ovum can travel through the peritoneal cavity and survive until the chorionic villi have created a new connection with the maternal tissue. This assumption is, a priori, unbelievable. Moreover, it is not supported by any clinical or embryologic observation.

Only two reports of such an occurrence are to be considered. Micholitsch in a case of fimbrial pregnancy found a placental polypus as an apparent remnant of the original implantation of the fecundated ovum in the Fallopian tube. Wallace, who had operated upon a patient with myoma complicated by tubal pregnancy, implanted the enucleated ovum in the bed of the likewise enucleated myoma and later observed the birth of a normal child at term. Both these cases could be interpreted as twin pregnancies.

On the other hand, the primary implantation of a fecundated ovum on the peritoneum is quite comprehensible as we know, from our investigations upon endometrioma, that the celom includes areas of cells not fully differentiated or else differentiated in the direction of endometrial tissue. That these areas are qualified for the primary implantation of a fecundated ovum is not only believable, but proved. I mention the communications of Dawson, Vara, Vozza, Frankel and Schenck, and myself.

In conclusion, I wish to point out that except for those cases where the placenta is retained in the reproductive tract while the fetus escapes into the abdominal cavity and continues there its life, there exists no real secondary abdominal pregnancy. All abdominal pregnancies in which the placenta or chorial villus is in intimate connection with the peritoneum are primary.

DR. ALFRED C. BECK.—The method of leaving the placenta in the abdomen without drainage was recommended by me in a paper which I read before the American Medical Association in 1918. This recommendation resulted from my experience with a full-term extrauterine pregnancy in which I attempted to remove the placenta and thereby started an alarming hemorrhage. The child not only survived but reached 22 years of age this year, and last month gave birth to a normal infant in the Long Island College Hospital. At that time, it also was my good fortune to see the grandmother who had the abdominal pregnancy twenty-two years ago.

DR. WILLIAM A. JEWETT.—The case of mine to which Dr. Lull has referred was kept under observation for many months following the operation, and the placental mass was found to decrease in size very slowly. It was palpable two years later on bimanual examination. Two and a half years after the operation for abdominal pregnancy I operated upon her for appendicitis and at that time examined the right adnexa, the site of the original implantation. I found a mass that was grossly similar to that of a chronic inflammatory disease. I removed this mass and had careful sections made for microscopic study but no evidence of placental tissue was to be found in the material.

DR. SAMUEL A. COSGROVE.—Dr. Lull has said that he hopes his experience will be a guide to the occasional operator. He has mentioned, however, the point that secundines left in the abdomen may not always resorb, and may become a source of subsequent trouble. With reference to the occasional operator, however, it should be emphasized that while different circumstances may indicate different types of management, the most desirable procedure in general is the closure of the abdomen without disturbing the placenta.

DR. WILLIAM E. STUDDIFORD.—I have seen one case which may be of interest in connection with the rate of absorption of the placenta in abdominal pregnancies, a patient who was operated upon at Bellevue Hospital in March, 1939. She had an abdominal pregnancy, the placenta being situated in a very fortunate position for follow-up. It covered the entire posterior portion of the pelvic peritoneum and the cul-de-sac. When the fetus was removed, the placenta was unavoidably disturbed, and profuse bleeding resulted, necessitating packing. The packing was removed without the disastrous consequences which Dr. Lull mentioned. This patient has been followed in the clinic ever since discharge in an effort to discover how long it took for the placenta to become absorbed. She was last seen in the clinic in January, I think, and a mass can still be felt in the cul-de-sac, although she has no symptoms whatsoever from its presence.

DR. LULL (closing).—Dr. Latzko may be correct in his feeling as to the existence of primary abdominal pregnancy. The authorities, however, in this country do not believe that it occurs and I have abided by their writings rather than my own opinion.

It is possible as Dr. Cosgrove suggests that I stress too much the point that the placenta does not always resorb. I did this because there is nothing in the literature that I can find on that aspect of the subject. I have endeavored, however, to impress the fact that the proper management of the live placenta is to let it alone. There is no question of this in my mind in spite of the fact that this one case gave rise to partial intestinal obstruction.

Dr. Studdiford brought up the very important question as to how long it takes the placenta to become absorbed. I am sure I would not have operated upon the last patient at the end of two months if she had not had the symptoms that she had and if the mass had not been increased in size.

### PREGNANEDIOL DETERMINATION AS AN AID IN CLINICAL DIAGNOSIS\*

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THE determination of the metabolism and excretion of progesterone, the corpus luteum hormone, has heretofore been impossible because there has been no accurate method for measurement of this substance either in the body or as an excretion product. Only small amounts of progesterone have been found in human urine or placenta<sup>1</sup> and from even as much as 50 Gm. of human corpora lutea only questionable amounts of progesterone have been obtained.<sup>2</sup> Five hundred cubic centimeters of blood from a pregnant woman has yielded negative results when tested by bio-assay methods.<sup>3</sup>

The discovery of pregnanediol, however, and its identification as an excretion product of progesterone has now enabled us to determine the presence of progestational activity with a fair degree of accuracy. Pregnanediol is found in the urine during the time and only during the time when the corpus luteum is generally considered to be active, i.e., during pregnancy and during the latter half of the menstrual cycle. It is excreted in the urine as sodium pregnanediol glucuronidate and in this form may be quantitatively measured according to a chemical method developed by Venning.<sup>4</sup>

#### METABOLISM AND EXCRETION

The metabolism of progesterone to sodium pregnanediol glucuronidate in the body is a complex procedure. The glucuronic acid complex is probably conjugated in the liver<sup>5</sup> and the whole compound is presumably excreted by the kidney, although no work has as yet been done to determine its presence in feces. Any abnormality in these structures causing inefficient metabolism or excretion may well result in a diminished or negative finding in the urine. It is possible also

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that progesterone may break down into other excretion products similar to pregnanediol, such as pregnanolone or allopregnanediol.<sup>6</sup> Heretofore it has been thought that the uterus was a necessary adjunct to this metabolic process. Browne and Venning<sup>7</sup> observed that progesterone injected into a hysterectomized woman was not excreted as pregnanediol. Hamblen and others<sup>8</sup> also observed this to be the case and further found that if a curettage were done during the luteal phase of the cycle, pregnanediol, which was present before, disappeared. He draws the conclusion from this procedure that endometrium is necessary to metabolize the product.

In this laboratory pregnanediol determinations were done on four women during and following the injection of 30 mg. of progesterone daily for three days. Three of these patients had had subtotal and one had had a total hysterectomy. Two of these patients excreted sodium pregnanediol glucuronide, as shown in Table I, whereas the other two had no excretion.

TABLE I

PATIENT	AGE	OPERATION	PROGESTERONE GIVEN	DAY GIVEN	PREGNANEDIOL FOUND
V. C.	49	Total hysterectomy Bilateral salpingo- oophorectomy	30 mg. 30 mg. 30 mg.	1	
				2	0
				3	0
				4	3.7 mg.
				5	0
G. T.	40	Subtotal hysterectomy and bilateral salpingo- oophorectomy	30 mg. 30 mg. 30 mg.	1	0
				2	0
				3	0
I. S.	32	Subtotal hysterectomy and unilateral salpingo-oophorectomy	30 mg. 30 mg. 30 mg.	1	
				2	0
				3	1.9 mg.
				4	1.3 mg.
				5	1.7 mg.
M. N.	38	Supravaginal hyster- ectomy and bilateral salpingo-oophorectomy	30 mg. 30 mg. 30 mg.	1	0
				2	0
				3	0

Furthermore, Buxton and Westphal<sup>9</sup> have found that men receiving injections of progesterone excrete large amount of sodium pregnanediol glucuronide. The uterus, therefore, is not considered a necessary adjunct to this metabolic process.

Since the metabolism of progesterone apparently involves a number of factors, an investigation was made of various laboratory animals in which it might be possible to study further the process. It was found that rabbits and cats excreted no pregnanediol either in their normal state or during pregnancy, and that monkeys excreted no pregnanediol even after injections of large amounts of progesterone.<sup>10</sup> Hartman and Marker<sup>11</sup> observed that no pregnanediol was excreted in the urine of pregnant monkeys.

#### EXCRETION IN PREGNANCY

The greatest yield and the purest form of pregnanediol is excreted during pregnancy in the human being. Since the excretion of this substance continues even after the removal during pregnancy of the ovary<sup>12</sup> containing the corpus luteum, it is surmised that the product is probably elaborated by the placenta.

Although there are great variations in the quantitative excretion of sodium pregnanediol glucuronide during pregnancy, the mean of daily excretions follows a definite curve.

Venning and Browne<sup>13</sup> followed nine pregnant patients daily throughout their period of gravidity and found values of from 4 to 10 mg. up to the sixtieth day of pregnancy. A rise then occurred, reaching a level of about 40 mg. at six months and a peak of 75 to 80 mg. in the eighth month.

Weil<sup>14</sup> observed that values were considerably lower than this in patients with toxemia of pregnancy, a finding confirmed by Browne and Venning.<sup>13</sup> It has been the common experience of workers with this material, however, that urine from toxemia patients emulsifies so extensively during the butyl alcohol extraction that it is difficult to keep from losing a certain amount of the substance. Also, it may be possible that, with the extensive water retention and decreased excretion of urine during toxemia, pregnanediol is withheld in the tissues.

No pregnancy cases have been observed here or reported elsewhere, which have had negative pregnanediol determinations. Consequently, so far as is known at present, a negative diagnosis of pregnancy may be considered very accurate by this method. In several hospital cases where the diagnosis of pregnancy was doubtful, this test has helped materially in reaching a definite conclusion. The two cases listed below are examples.

J. H., aged 27 years, a patient with a history of severe toxemia of pregnancy, had previously delivered a macerated fetus and had had a therapeutic abortion done because of toxemia. At the time of admission to the hospital on March 29 she gave a history of menstruating last on February 6. Because of history of previous severe toxemia, therapeutic abortion was decided upon. She bled a little on the evening of March 29, however, and a question arose as to a definite diagnosis. Urine was taken for both Aschheim-Zondek test and pregnanediol determination on April 1. The Aschheim-Zondek test was positive but no sodium pregnanediol glucuronide was found in the urine. However, since the Aschheim-Zondek test was positive, a laparotomy for termination and sterilization was decided upon. There was no evidence of pregnancy. In this case there apparently had been a spontaneous abortion the night of admission to the hospital. Very possibly pregnanediol disappears from the urine following the termination of pregnancy more quickly than does the prolactin searched for in the Aschheim-Zondek test.

Another patient, E. H., aged 27 years, had had four previous miscarriages. When she was about three and one-half months pregnant, a pregnanediol determination was done because she had had occasional periods of spotting and a question arose as to the possibility of there being an inherent corpus luteum deficiency. No pregnanediol was found in the urine and examination disclosed that the patient was not pregnant. She had either never been pregnant or had aborted. No thorough pelvic examination had been done previously for fear that manipulation might start further bleeding. As a matter of fact, a careful investigation of this patient's past history disclosed no proof that she ever had been pregnant, either on this occasion or the previous ones, and this case cannot actually be considered one of repeated abortion.

On the other hand, the positive diagnosis of pregnancy from pregnanediol content in the urine is not so easily determinable. Wilson, Randall and Osterberg<sup>16</sup> consider the finding of 10 mg. or more of pregnanediol in the urine following a missed period diagnostic of pregnancy, and a smaller amount in a patient with previously regular periods highly suspicious. The fact that a patient may, however, be having a delayed menstrual period must be considered.

Such a case is A. B., aged 40 years. Her last menstrual period was Dec. 7, 1938. She had slight bleeding in February and in March came to the clinic complaining of amenorrhea, nausea, and vomiting. Physical examination disclosed a number of fibroids increasing her uterus to the size of a four months' pregnancy. Her Aschheim-Zondek test was negative. Pregnanediol determination was 3.5 mg. She was operated upon for removal of the fibroids and the endometrium was found in the secretory phase with no evidence of decidua or trophoblast. This woman was probably undergoing the menopause and had one episode of delayed ovulation and menstruation. From this instance it will be seen that the presence of amenorrhea and pregnanediol simultaneously is not diagnostic of pregnancy.

Twenty pregnanediol determinations have been made in correlation with Aschheim-Zondek or Friedman tests in cases of suspected pregnancy in order to determine the accuracy of the two methods. Ten of these patients were proved to be pregnant by confirmatory findings in both Aschheim-Zondek and pregnanediol determinations, varying amounts of the latter being found in all cases, whereas in the ten cases with negative Aschheim-Zondek findings, no pregnanediol was present in the urine.

#### EXCRETION IN CASES OF HABITUAL ABORTION

Progesterone has been extensively used in the treatment of habitual abortion, on the theory that the cause of habitual abortion is insufficient progestational activity.<sup>17-19</sup> Since heretofore there has been no method of measuring progestational activity, the treatment of these cases with progesterone has been theoretical.

It was therefore thought advisable to carry out pregnanediol determinations during early pregnancy on several patients with a history of three or more previous spontaneous abortions. Careful investigation of many of these cases revealed that the great majority of patients had only an indefinite history of abortion. There was no definite proof of pregnancy and the periods of amenorrhea which made the diagnosis of pregnancy probable were usually of only two to three weeks' duration. There were rarely a curettage and pathologic examination of the specimen.

Five patients in whom there was an accurate history of three or more spontaneous abortions were studied during early subsequent pregnancy, and they all excreted pregnanediol commensurate with normal amounts for their period of gravidity. One of these patients subsequently aborted again, however, and her history is given below.

B. P., aged 37 years, married twelve years with past obstetric history as follows: July, 1928, spontaneous abortion, three months; December, 1931, spontaneous miscarriage, six months; September, 1933, spontaneous abortion, three months; March, 1937, spontaneous miscarriage, five months; July, 1939, spontaneous abortion (Friedman positive), six weeks. The patient's past medical history, physical examination, and laboratory findings were essentially negative. The basal metabolic rate was -8; the Wassermann negative.

She had a normal period on September 9, did not menstruate in October and on October 20 her Friedman test was positive. Her further history is represented graphically in Fig. 1.

It will be observed that even unusually large amounts of progesterone did not maintain an adequate progestational activity as measured by pregnanediol excretion, and she aborted spontaneously in the third month of her pregnancy. After injection of over 100 mg. of progesterone

in three weeks, two determinations showed from 3 to 4 mg. of pregnanediol to be present, an amount which would be found in a castrate following injection of this amount of progesterone. In other words, this woman was apparently producing no progesterone, either from the corpus luteum or the placenta, or if she was, it was not being excreted as pregnanediol glucuronidate. Also large amounts of artificially supplied progesterone were insufficient to maintain pregnancy. It is therefore assumed that some pathology was present in the placenta which not only prevented the production of progesterone but also prevented adequate nidation or nutrition of the trophoblast. The assumption may also be made that, if progesterone was being supplied, its utilization was in some way being prevented.

Repeated pregnanediol determinations in cases of threatened or habitual abortion may, therefore, give us a fairly definite indication as to whether or not the patient will continue with the pregnancy investi-

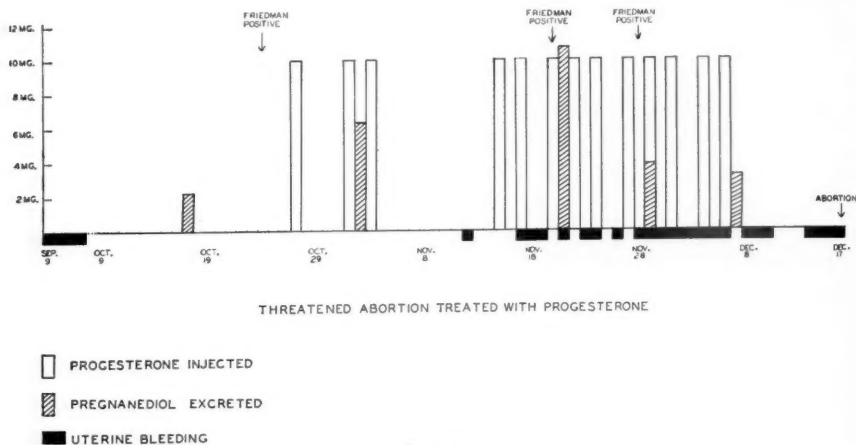


Fig. 1.

gated. They also give us some indication as to whether or not progesterone administration is being utilized by the organism. In the case presented above, the administered progesterone was apparently not being utilized and consequently its administration as a therapeutic agent was of no value.

#### EXCRETION IN NORMAL WOMEN

In the normal nonpregnant woman the excretion of sodium pregnanediol glucuronidate has been found by us to occur only during the latter half of the menstrual cycle. It must be said, however, that the great majority of assays have been done only on the urine of the latter half of the menstrual cycle. Those done during the first half of the cycle have been incidental and consist of 11 determinations only, but none has contained sodium pregnanediol glucuronidate.

Venning and Browne<sup>7</sup> studied the excretion of 10 patients through one or more cycles. So far as was possible, they determined the occurrence of ovulation by means of ovulation pain, intermenstrual bleeding, and the occurrence of gonadotropic hormone in the urine, all of which are probably inaccurate. They found pregnanediol present twenty-four to forty-eight hours after these various "signs" of ovulation, although this was not always the case. Its excretion in-

creased until about one week before menstruation, then fell off toward the end of the cycle and stopped abruptly, menstruation ensuing one to three days after the disappearance of pregnanediol. Although they found great variation in corpus luteum activity as measured by total pregnanediol excretion in one period, the total amount varying from 3 to 54 mg., they maintained that once the product was found, excretion continued without interruption until it stopped before the period. Pratt and Stover<sup>21</sup> also found this to be the case, but this has not been the experience in our cases or in the series published by Hamblen and others.<sup>8</sup>

In doing random pregnanediol determinations during the last two weeks of the menstrual cycle on patients with regular menstrual periods, it was observed that occasionally no pregnanediol was found. Consequently daily determinations were done on three supposedly normal women. One of these women excreted no pregnanediol at any time during the two weeks before one period. The other two excreted amounts varying from 2.2 mg. to 7.5 mg. but there were occasional days during the period of excretion when they excreted none. A graphic representation of their excretion is shown in Fig. 2.

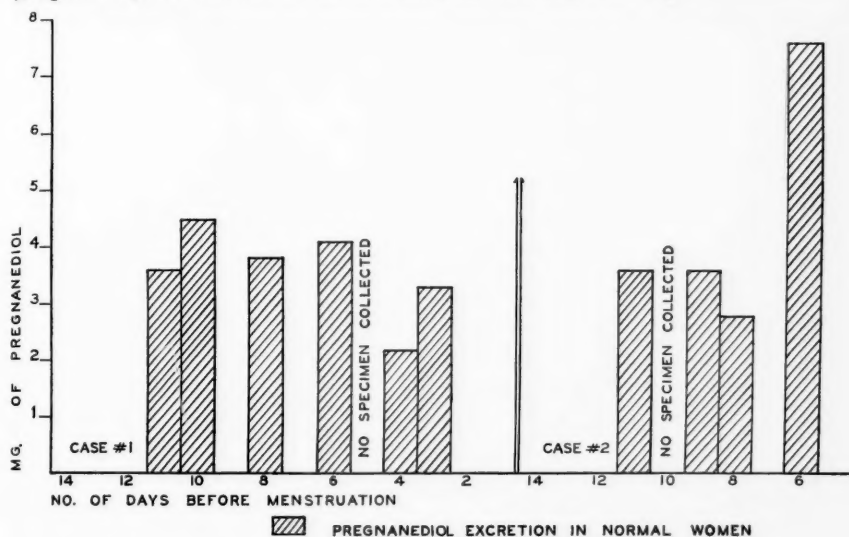


Fig. 2.

It will be observed that the amount of excretion varies considerably from day to day and according to no particular rule, but that there have been no instances of more than a one-day lapse during the period of excretion. Whereas in our procedures twenty-four-hour specimens were tested, Browne and Venning took forty-eight-hour samples, which may explain the discrepancy in results. This is an important differentiation, because, if it is true that a patient may normally skip a day during a normal period of excretion, one twenty-four-hour specimen taken as a diagnostic test of corpus luteum activity may not necessarily be accurate.

#### CORRELATION OF PREGNANEDIOL EXCRETION WITH ENDOMETRIAL BIOPSY FINDINGS

It has been generally considered heretofore that the presence of corpus luteum activity presupposes the phenomenon of ovulation.<sup>22</sup>



This is probably the case under normal conditions, but it is possible that corpus luteum formation may occur without extrusion of the ovum. The presence of an ovum trapped within the interstices of the corpus luteum has been observed in monkeys<sup>23</sup> and therefore this may possibly occur in the human being. Consequently, evidence of corpus luteum activity in the form of secretory endometrium or pregnanediol content of the urine is only *prima facie* evidence that ovulation has occurred. It is mainly evidence that there is corpus luteum activity present. It may be presumed that ovulation has occurred, and because corpus luteum formation after ovulation is probably the usual sequence of events, the presumption is quite valid.

In order to correlate the presence of pregnanediol in the urine with evidence of luteal change in the endometrium, Wilson, Randall and Osterberg,<sup>16</sup> at the Mayo Clinic, obtained coincidental pregnanediol determinations and endometrial biopsies on 50 patients complaining of various gynecologic conditions. No pregnanediol in significant amounts was found in their cases in which specimens were taken during the proliferative phase of the cycle. Two cases were reported which did have less than 2 mg. present. No melting points were given for these determinations, a procedure which should be routinely followed, due to the many possible errors in the extraction process. Consequently, the significance of these two cases is doubtful. Of the determinations done at the time the endometrium, as shown by biopsy, was in the early or late differentiative, or secretory phase, there were many which contained no pregnanediol. This finding has also been observed by us, and will be discussed later.

Seventy-eight pregnanediol determinations were done in this laboratory on patients who at the same time were subjected to endometrial biopsy or operation for various causes, most of the biopsies having been taken in the sterility clinic. Of these 78 combined determinations, 65 have sufficient records so that the time of their next menstrual period may be accurately determined. All of these biopsies except two were taken during the last two weeks of the menstrual cycle.

Forty-five of these biopsies showed secretory endometrium. Urine determination for pregnanediol done at the same time or within a day or two of biopsy showed that 31 of the 45 had pregnanediol present in varying amounts, the smallest being 1.1 mg., the largest being 10.2. Of the 14 which had no pregnanediol present, 12 determinations were made within two days of menstruation, when none would be expected normally, 2 were done at times in the cycle when pregnanediol should be present. This finding will be discussed later.

Fifteen of the biopsies showed proliferative endometrium, all except two having been taken during the latter half of the cycle. No pregnanediol was found on coincidental urine determinations.

Five biopsies had questionable diagnoses and no definite decision could be made as to whether these were definitely proliferative or secretory. Coincidental urine determinations showed 0 pregnanediol in 3 cases, 2.7 mg. in one, and 4 mg. in one.

The absence of pregnanediol in the urine during the latter half of the cycle when secretory endometrium is present may be explained in several ways. In the first place, as has been stated previously, the substance disappears from the urine one or two days before menstruation under normal conditions, so that within this time limit pregnanediol absence in the presence of secretory endometrium may be considered physiologic. Also, in doing daily determinations on normal women it has been shown, as previously stated, that occasionally they skip a day

during the excretory period. It must be stated that errors in collection, hydrolysis of the specimen, and errors in the technique of the determination must be kept in mind as possible explanations. Since only 2 of the 45 determinations done during the secretory stage showed no pregnanediol at the time when it should be present, these explanations seem adequate.

Table II shows graphically the relation between biopsy diagnosis and pregnanediol determination.

TABLE II. ENDOMETRIAL BIOPSY AND PREGNANEDIOL

BIOPSY DIAGNOSIS	NO.	PREGNANEDIOL PRESENT	PREGNANEDIOL ABSENT
Secretory	45	31	14 (12 within 2 days of menstruation)
Proliferative	15	0	15
Undiagnosed	5	3	2
Total	65	34	31

This series would indicate then that progesterone is excreted in the urine as sodium pregnanediol glucuronidate during the time that the endometrium is being activated to the secretory phase. It is, therefore, a valuable diagnostic adjunct in determining ovulation, especially since we feel that the endometrial biopsy may not always be accurate. Ten years ago Bartelmez<sup>24</sup> mentioned the fact that different parts of the uterine mucosa responded differently to either vascular or hormonal influences, and we have observed in biopsies taken with the small Meigs curette bits of endometrium from the same uterus which were considerably different in character. At least two biopsies have shown both proliferative and secretory characteristics from the same mucosa.

Whether different endometriums, or the same endometrium in different areas, may vary in their progestational responses is a question discussed by Wilson, Randall and Osterberg.<sup>16</sup> Because of the great quantitative discrepancy in pregnanediol output in apparently normal women, they feel that some endometriums may need considerable progestational stimulation to undergo secretory changes, whereas others need only a small amount, in fact so little that the metabolic product, pregnanediol, may not even appear in the urine. They do not consider, however, the necessity for estrogenic proliferation of the endometrium, which must occur before secretory changes may take place, nor the fact that estrone acts concurrently with progesterone in the formation of a secretory endometrium.<sup>25</sup>

There are so many variables in the process of progesterone metabolism and pregnanediol excretion that the amount of pregnanediol secretion cannot be considered any indication of the amount of progestational activity in the organism. It has been stated previously that the liver and kidney and other unknown factors all have a part to play in this transformation and excretion. Obviously, deficiency in any of these organs would result in decreased excretion without necessarily affecting the utilization and secretion of progesterone itself. In the second place, the mechanical factors involved, such as the collection of the urine and its preservation, and the technique of the process itself, make the quantitative result quite variable.

Unfortunately, therefore, conclusions drawn from the interpretation of differences in the *quantitative* excretion of pregnanediol are undependable.

#### SUMMARY

1. Pregnanediol is defined as an excretion product of the corpus luteum hormone progesterone.

2. Its synthesis as sodium pregnanediol glucuronidate probably occurs in the liver. Its metabolism and excretion are not dependent upon the uterus or ovaries, as is shown by injection experiments on men and hysterectomized women.

3. The urine of monkeys, cats, and rabbits does not contain pregnanediol either normally, during pregnancy or after progesterone injections.

4. The greatest yield and purest form of pregnanediol glucuronidate occurs in the urine of pregnancy. No pregnant patients have been observed who do not excrete pregnanediol glucuronidate. Therefore the negative diagnosis of pregnancy may be made as a result of negative pregnanediol determination.

Pregnanediol is present in small amounts in the urine during the latter half of the menstrual cycle in normal women. Although the excretion during pregnancy is greater than that during the luteal phase of the menstrual cycle, a diagnosis of pregnancy cannot be made on this basis because the quantitative determination is not sufficiently accurate.

5. Five cases of habitual abortion were tested for pregnanediol excretion during subsequent pregnancies. One of these patients aborted spontaneously during the course of progesterone therapy. She showed unusually low pregnanediol excretion.

6. Seventy-eight simultaneous pregnanediol determinations and endometrial biopsies were done on patients, most of whom were in the sterility clinic. These tests were done in order to ascertain the accuracy of these two methods of determining progestational activity. It is apparent that pregnanediol is excreted during the time that the endometrium is being activated to a secretory phase and only during that time.

7. There are so many factors controlling the excretion of pregnanediol glucuronidate that the quantitative result is liable to variation. Therefore diagnosis cannot be made on a basis of *quantitative* differences in excretion.

I wish to express my gratitude to Dr. B. P. Watson, Chief of the Sloane Hospital for Women, and to Dr. Earl T. Engle, Department of Anatomy, College of Physicians and Surgeons, Columbia University, for their helpful advice and suggestions during the course of this study.

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## THE USE OF SULFANILAMIDE IN OBSTETRICS AND GYNECOLOGY

### A REPORT ON 121 CASES

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IN NOVEMBER, 1939<sup>7</sup> we reported the results of sulfanilamide therapy in 118 patients with severe puerperal infections of the genital tract, 83 intrapartum or post-partum cases, and 35 cases of postabortal infection. Though careful bacteriologic investigation was carried out in most of these cases, treatment was not based on isolation of the *Streptococcus hemolyticus*. It had seemed probable from the work of Colebrook and his co-workers<sup>2-4</sup> that little could be expected outside this group, yet clinical response in the entire series was convincing in 45 cases, or 38 per cent, and satisfactory though not so prompt in another 45 cases. We believe that in 76 per cent of these severe cases, sulfanilamide therapy was an important factor in the patient's recovery.

Since the prognosis of severe puerperal infection is grave, and the use of sulfanilamide involves no abandonment of any specific form of treatment, chemotherapy is indicated and need not depend entirely upon identification of the *Streptococcus hemolyticus*. In intrapartum infection, too, sulfanilamide has been given before report of the vaginal culture taken at the same time. Its hazards are definite but none of them need be serious if control is adequate. Though culture is routine in all post-partum patients whose temperature reaches 100.4° F., we have not treated minor febrile disturbances with sulfanilamide.

### MATERIAL

Since our first report, 27 patients with severe puerperal infections have received sulfanilamide. It is so difficult to define the anatomic limits of these infections that cases have been classified clinically as severe by the same standard as heretofore; (1) high initial rise of temperature; (2) spiking temperature; (3) peritonitis; (4) chills; (5) spreading inflammation. Temperature ranged from 101° to 102° F.

in 3 cases, from 102° to 103° in 4 cases, from 103° to 104° in 16 cases, and from 104° to 106° in 4 cases. Cases in the lowest temperature group were included because of other evidence of the severity of the infection. None of these patients had a positive blood culture. Five were intrapartum infections in three of which the temperature rose to 102° to 103° F. Two patients had peritonitis, and in two others pyelitis appeared to be associated with genital tract infection. A four-hour day and night schedule of 20 gr. of sulfanilamide was maintained through the night for two to six days in 24 cases, and eight, ten, and twelve days in 3 cases.

The clinical response to sulfanilamide therapy was good in 21 cases, doubtful in 5 cases and negative in 1. There were no deaths. In only one of the doubtful result cases had the streptococcus been identified. In 7 cases in which *Streptococcus hemolyticus* was demonstrated, results were good. In 6 out of 7 cases in which a streptococcus not positively identified as beta hemolyticus was found, and in 2 cases in which a nonhemolytic streptococcus was isolated, results were good. In 7 cases in which no streptococci were found, results were good in only 1. Streptococci were found in 16 cases and other organisms were rarely seen; *B. coli* in 2 cases, *B. proteus* in 1 case, and *Staphylococcus aureus* in 1 case. In 5 intrapartum infections response to sulfanilamide was doubtful in 1, and good in 4 cases in 2 of which *Streptococcus hemolyticus* was reported later.

#### COMMENT

These results are better than those we have previously reported and are additional evidence that sulfanilamide finds its greatest indication in *Streptococcus hemolyticus* infections. In severe infections sulfanilamide therapy need not wait upon bacteriologic investigation, yet this information is of some importance in deciding whether the drug should be continued in the absence of favorable clinical response. Sulfanilamide should not be used at all in mild cases of infection as it is unnecessary and probably useless. Douglas<sup>5</sup> has found the hemolytic streptococcus in less than 1 per cent of puerperal infections, and insists that, with very few exceptions, accurate bacteriologic diagnosis before the commencement of therapy is all important. In severe infections, however, the problem is different, since the hemolytic streptococcus is the infective agent in a large number of these cases. Fry<sup>6</sup> found that 33 per cent of all severe cases, and 70 per cent of all fatal cases were due to this organism. Group A does not include all the hemolytic streptococci pathogenic for man, for one of us (A. H. R.<sup>9</sup>) has reported two deaths in our service due to Groups B and C. Sulfanilamide failed in both cases, and in vitro and in vivo experiments indicated that it has no effect on these strains. So far as we know, all the strains of Group A respond to sulfanilamide therapy, but evidence in the case of infection by anaerobic streptococci, *Streptococcus viridans*, nonhemolytic streptococci, staphylococcus and *B. coli* is inconclusive. Time is an important factor in combating severe puerperal infection.

#### PYELITIS

We have given sulfanilamide to 17 patients with pyelitis, 12 ante-partum and 5 post-partum cases; 6 were primiparas and 11 multiparas. The dose of sulfanilamide in most cases was 20 gr. every four hours, but fluids were not definitely limited; titers ranged from 3.1 mg. to 8.5 mg.

Chills occurred in 8 cases, all ante-partum, though the highest temperatures were noted in the post-partum group, 2 reaching 104.4° F. In 10 cases temperature reached 103° F. In 2 cases there was no fever, but diagnosis was made on lumbar pain, kidney tenderness, and pyuria.



Toxemia was present in 3 cases. In 2 of these the patient was admitted for toxemia and developed pyelitis on the ward. In the third case, although the patient was admitted for pyelitis, she had been admitted for toxemia earlier in the same pregnancy. In the other 11 cases there was no evidence of toxemia or diminished renal function; urea clearance, Fishberg and blood chemistry tests were repeatedly done.

In the 17 cases, blood culture was positive for a gram-negative bacillus in 1, and the urine was cultured in 13 cases and found positive in 11. *B. coli* was found in 8 cases, associated with a nonhemolytic streptococcus in 2, with *B. proteus* 1, and *Staphylococcus aureus* 1; other organisms were nonhemolytic streptococcus 1, *B. proteus* 1, pneumococcus 1.

Respiratory infection was present in 4 cases, pharyngitis 2, bronchitis 1, and bronchopneumonia 1. In this case the pneumococcus was cultured from the urine. This patient, admitted in the eighth month of pregnancy for bronchopneumonia and pyelitis, responded well in two days to 160 gr. of sulfanilamide. She was readmitted the day after discharge with pyelitis more severe than the first infection, temperature reaching 105.6° F. with repeated chills. She again responded to sulfanilamide therapy. In the other 3 respiratory infections with pyelitis, *B. coli* was cultured in the urine of 2 cases, and a nonhemolytic streptococcus in 1.

The 5 post-partum cases did well with sulfanilamide. Detailed clinical data in 12 ante-partum cases are tabulated in Table I.

TABLE I. SULFANILAMIDE THERAPY—ANTE-PARTUM PYELITIS

	PERIOD OF GESTATION MONTHS	SULFANILAMIDE			RECURRENCE OF PYELITIS
		GRAINS GIVEN	DAYS GIVEN	RESULTS	
1	5	240	3	Good	Not yet delivered
2	Term	480	5	Good	
3		755	9		Two recurrences in seventh month
	7	390	6	None	
	7	580	7		
4	8	400	4	Good	Not yet delivered
5	6	460	6	Good	
6	7	360	3	None	Two recurrences post partum
7	5	240	4	None	
	7	380	4		Two recurrences, seventh month and post partum
8	8	160	2	None	
9	6	200	2	Good	Recurring post partum Pyelitis 2 yr. previous
10	8	120	2	Good	
11	Term	540	6	Good	Previous pyelitis
12	5	240	2	Good	

Infection of the urinary tract is a common complication of pregnancy. Pyelonephritis is serious and may cause death. Coliform bacilli are the usual infective agents, yet here as elsewhere other organisms may cause severe infections, and should be thought of when pyelitis is associated with upper respiratory infection. The objectives of treatment are urinary antiseptics and relief of stasis. Intravenous pyelography and cystoscopy should be reserved for intractable cases. Fortunately most infections improve on any type of treatment, even bed rest alone. Subsidence of symptoms does not mean cure, nor is a sterile urine culture a satisfactory criterion. Long follow-up, perhaps only through another pregnancy, is necessary. In our small group of 12 ante-partum cases, with 3 as yet undelivered, pyelitis has recurred during the same pregnancy or in the puerperium in 4. In all probability recurrence may be expected in this group.

One patient in this group with severe pyelitis in the third month responded well to 755 gr. of sulfanilamide over a nine-day period. On readmission in the seventh month with another severe attack, she was given 390 gr. in six days and her symptoms disappeared, but recurred three days later; she was then given 580 gr. during the next seven days. Shortly afterward she was delivered prematurely, showing no recurrence in the puerperium.

We have evaluated our results by the clinical course of the patient, not from determination of bacilluria, though that should be helpful. The immediate response has been good, occasionally dramatic, for in 13 of our 17 cases subsidence of symptoms was rapid. Sulfanilamide would appear to be indicated, since it is excreted almost entirely by the kidneys, quickly diffusing into tissues flooded with urine. Concentration should occur with limited fluid intake. Our limited experience however indicates that it is but little better than other methods of treatment. We have not used chemotherapy in mild gynecologic infections of the urinary tract due to catheterization or contiguity as they seem to be self-limited.

#### MASTITIS

Mastitis, as a rule, is a mild infection yet it may be severe. The infective agent cannot be demonstrated unless suppuration occurs. If the breast fails to respond quickly to the ordinary treatment, sulfanilamide may be given with hope of success. We have given it to but 3 patients. It deserves consideration.

#### SEVERE PELVIC INFECTION (NONPUERPERAL)

For practical purposes pelvic inflammation is of puerperal origin or due to gonorrhea or instrumentation, though it may occur, of course, as a result of extension of infection outside the genital tract. A large number of acute infections become chronic. The characteristic lesion of pelvic gonorrhea is the pyosalpinx, with or without involvement of the ovary. Cellulitis is usually due to the streptococcus, staphylococcus or *B. coli*, and rarely to the gonococcus alone. Severe re-infections or exacerbations occur rarely in the typical cellulitic lesion, but are common in mixed infections. Studdiford, Caspar and Seadron<sup>10</sup> have shown that gonococci may survive in the tubes for many years. It is likely that anaerobes play but a small part in the absence of necrotic tissue, and since Fry<sup>6</sup> has shown that the normal genital tract is not a favorable situation for survival of *Streptococcus hemolyticus* Group A, the presence of these organisms depends upon instrumentation or previous puerperal invasion.

The management of 450 to 500 cases of pelvic infection admitted yearly to our gynecologic wards is our most formidable problem. Surgery as a rule is not indicated, and we have operated only for prolonged and increasing menorrhagia, severe dyspareunia of long standing, and serious disability. Partial operations are rarely curative, but treatment of external foci of infection is of great importance. We have learned to recognize ovarian abscess as a serious complication, and so drain it rather promptly. Cellulitis yields but little to conservative treatment. In fact our entire experience with treatment such as foreign proteins, diathermy, Elliott treatment, transfusions and the like has been very discouraging. Iontophoresis, however, seems promising. Since January, 1938, we have given sulfanilamide therapy a trial, hoping for good results, yet expecting little in the resolution of hard fibrotic or cellulitic lesions, since diffusion of the drug into these tissues should be difficult. As yet we have not used it in chaneroid infection or lymphogranuloma.

Early in our work sulfanilamide was given in doses of 80 gr. a day for two days, 60 gr. daily for the next three days, and 40 gr. daily thereafter (39 cases), or 120 gr. a day for two days, 80 gr. daily for the next three days, and 60 gr. a day thereafter (24 cases). Later it was administered in 20 gr. doses every four hours day and night with restriction of fluids. Blood titers have been fairly consistent.

In reporting 74 cases we have included 13 from the service of Dr. Alfred C. Beck at the Long Island College Hospital\*; 27 patients were white and 47 negro. All infections were severe enough for hospitalization. As clinical evidence of severity, 46 patients had single or bilateral pelvic masses; fever of 101° to 105° F. was present in 60 cases, with temperature of 103° to 105° F. in 31 cases; general peritonitis was present in 1 case, and marked pelvic peritonitis in 21. In 23 cases external lesions of gonococcal infections as urethritis, Skenitis, and Bartholinitis were seen, and in 4 cases acute cervicitis. Smears for the gonococcus were positive in

\*We are indebted to Drs. Harvey B. Matthews, William A. Jewett, and George W. Phelan for these cases.

13 cases, and complement fixation was positive in 26. In 15 cases apparently of gonorrheal origin complement fixation was negative, yet smears were positive in 3.

## DIAGNOSIS

Acute exacerbation of chronic pelvic inflammation		30
Salpingo-oophoritis (includes the above)		56
With pelvic peritonitis	21	
With general peritonitis	1	
Cellulitis		4
With salpingo-oophoritis		5
With salpingo-oophoritis and pelvic abscess		2
With peritonitis		1
Abdominopelvic abscess		3
Abdominopelvic abscesses (multiple)		3

The age of these patients is of interest, as in our experience incidence of chronic pelvic inflammatory disease diminishes as women grow older, and its lesions usually become symptomless or cured with menopause; 56 were less than 35 years of age, 7 between 35 and 40, 9 between 40 and 45, and 2 between 45 and 50. None had passed the menopause; pelvic masses or fever rarely occur in postmenopausal gonorrhea. The age of the infection may, as a rule, be determined with fair accuracy from the history.

## AGE OF THE INFECTION

Less than 3 months	22
3 months to 1 year	6
1 year to 4 years	12
4 years or longer	12
Old infection (age unknown)	8
Not determined	14

On the whole, results were disappointing. Chemotherapy was unsatisfactory in cellulitic infections and abdominopelvic abscess, somewhat successful in acute exacerbations of chronic pelvic inflammation, and satisfactory only in cases of primary gonococcal infection. But even in primary gonorrhea it was impossible to predict good results with any certainty. A brief discussion of a few typical cases will illustrate.

*A. Cellulitic Infection.*—H. K., aged 18 years, had a huge cellulitic mass, and the etiology was obscure. She received 725 gr. of sulfanilamide with no effect on her severe septic course or on the size of the exudate.

*B. Abdominopelvic Abscess.*—(1) I. F., aged 31 years, negress, had been operated upon for salpingitis five years previously. She presented on admission a large tuboovarian abscess with septic temperature often reaching 104° F.; sulfanilamide failed and she improved only after colpotomy.

(2) J. A., aged 32 years, who had been operated upon for ovarian abscess seven years before admission, was admitted with abdominopelvic abscess and septic temperature. She became worse under therapy but recovered after abdominal drainage of two abscesses at two independent operations.

(3) E. C., aged 41 years, had a pelvic infection with gonococcal smear positive; 600 gr. of sulfanilamide were given in 7 days. She became worse, developing a pelvic abscess which was drained vaginally; pus showed a pure culture of *Staphylococcus aureus*. Death occurred one day later.

*C. Primary Gonococcal Infection.*—(1) O. G., aged 24 years, negress, had acute salpingitis with positive gonococcal smear; 530 gr. of sulfanilamide were given in seven days with striking improvement. Temperature which had been 102° F. for two days became normal the day after chemotherapy was begun and remained so.

(2) E. B., aged 28 years, negress, was admitted with a temperature of 104° F., Skenitis, Bartholinitis, and small tender adnexal masses. She responded well to 765 gr. of sulfanilamide, temperature becoming normal and smears negative.

(3) M. V., aged 25 years, negress, had a vulvovaginitis and salpingo-oophoritis. She was given 525 gr. of sulfanilamide in seven days without much improvement. Smears remained positive, though blood titers reached 11.8 mg. and 11.3 mg.

(4) D. W., aged 19 years, was admitted with gonococcal urethritis, cervicitis, and pelvic pain but no fever. She received 585 gr. of sulfanilamide in eight days. On the seventh day however, temperature rose to 104° F., with evidence of severe pelvic peritonitis. Since sulfanilamide had failed to stop progress of her infection under optimal conditions, it was discontinued. She improved slowly, smears remaining positive three weeks after admission.

TABLE II. RESULTS OF THERAPY

	TOTAL NO. OF CASES	SATISFAC- TORY	DOUBTFUL	UNSATIS- FACTORY
Cellulitic infection	12	1	3	8
Abdominopelvic abscess	6	1	1	4
Primary gonococcal in- fection	11	6	2	3
Acute exacerbation of chronic disease	30	5	16	9
Difficult to classify	15	4	9	2
	74	17 -23%	31	26

It is impossible to set up proper control series for these types of infection. Evaluation of therapy is based on the course of the patient in the hospital. It is common experience to see patients improve on bed rest alone, even with resolution of inflammatory masses. We could easily show such a series. Unusually rapid subsidence of fever, disappearance of abdominal tenderness and rigidity, relief from pain and diminution in size of pelvic masses were our criteria of satisfactory response to chemotherapy. When the clinical course of the disease coincided with previous experience, it was difficult to assess the value of therapy, so we have called this result doubtful. When the patient did not improve or became worse, obviously sulfanilamide was without value.

Reports of gynecologic infections other than primary gonococcal infections are scant and limited to but few cases. Grodberg and Carey<sup>8</sup> have reported resolution of tuboovarian masses in ten to fourteen days. Bomze, Fuerstner and Falls,<sup>1</sup> in 45 cases treated in the out-patient clinic, observed resolution of large inflammatory masses in 3 cases after four to six weeks. In Douglas<sup>5</sup> gonorrhea cases, only 1 had inflammatory pelvic disease with masses.

Our failure with chemotherapy in pelvic inflammation of long standing is not surprising. Success depends upon the nature of the organism, proper concentration of the drug in the blood and easy diffusion into the diseased tissues. We are also impressed with the failure of chemotherapy, in our experience, in puerperal infection with vegetative endocarditis, or when placental fragments or polyps are present in the uterus. Thus the character of the lesion is of great importance. We have observed no notable diminution in the size of pelvic masses. A satisfactory result in 74 cases occurred in but 17, and in 11 of these, success was probably due to the presence of the gonococcus. However only 6 out of 11 primary gonococcal infections responded satisfactorily. No doubt this is the best form of therapy we have and failure or sharp re-invasion while under treatment is probably due to the presence of nonspecific organisms. Cultures as evidence of cure are no doubt superior to smears, as Douglas<sup>5</sup> points out. Complement fixation has a practical value in that persistence of a strongly positive reaction indicates a latent focus, even though cultures are negative. Cellulitis and the common fibrotic and cystic changes occurring in tuboovarian masses cannot reasonably be expected to respond to sulfanilamide therapy. The most enthusiastic advocates of chemotherapy in the male admit its failure in nonspecific prostatitis and epididymitis. These lesions correspond to the common form of inflammatory tuboovarian masses in the female, for in the genital adnexa of both sexes, nonspecific organisms follow the invasion of the gonococcus, and accumulations of pus surrounded by fibrotic tissue will not permit diffusion of the drug.

## TOXIC MANIFESTATIONS

There were no deaths due to sulfanilamide therapy. Toxic symptoms were noted as in our previous series of 118 cases in about half of the cases. One case of acute hemolytic anemia occurred in a sixteen-year-old negress with primary gonococcal infection, after administration of 330 gr. of sulfanilamide, 120 gr. on the first and second days, and 90 gr. on the third, when the hemoglobin dropped from 65 per cent Sahli to 55 per cent; chemotherapy was discontinued, but three days later hemoglobin was 24 per cent; she responded well to transfusions. The appearance of jaundice and increased amounts of urobilin may exceptionally be preceded by actual hemoglobinuria. We have not seen agranulocytosis as it apparently occurs only after longer treatment than we have thought wise. We have observed jaundice in three cases without confirmatory evidence of hemolytic anemia; in one of these patients with considerable tenderness over the liver, it was thought to be due to toxic hepatitis, the icterus index reaching 143 units.

Our complete clinical results in obstetrics and gynecology are shown in Table III.

TABLE III. CLINICAL RESULTS OF CHEMOTHERAPY IN OBSTETRICS AND GYNECOLOGY  
121 SEVERE INFECTIONS

INFECTIONS	TOTAL NO. OF CASES	RESPONSE TO SULFANILAMIDE		
		GOOD	DOUBTFUL	NONE
<i>Puerperal:</i>				
Post partum	22	17	4	1
Intra partum	5	4	1	—
Pyelitis	17	13	—	4
Mastitis	3	—	—	—
<i>Gynecologic:</i>				
Cellulitis	12	1	3	8
Abdominopelvic abscess	6	1	1	4
Primary gonococcal infection	11	6	2	3
Exacerbation of chronic pelvic infection	30	5	16	9
Unclassified pelvic infection	15	4	9	2
Total	121			

## CONCLUSIONS

In minor febrile disturbances chemotherapy should not be used. In severe intrapartum and puerperal infections of the genital tract, sulfanilamide should be given provided the patient is in a hospital where its administration may be properly controlled. Bacteriologic diagnosis need not precede therapy, yet early recognition of the infective agent is important. Since it is probable that sulfanilamide is effective only when the *Streptococcus hemolyticus* Group A is present, administration should not be continued for longer than a week, if another organism has been isolated.

In mastitis not responding to ordinary treatment, chemotherapy should be tried. In pyelitis it is at least as effective as other methods of drug treatment. A large series of cases followed over a considerable period of time will be necessary before positive statements can be made.

Sulfanilamide should be used in gynecologic infections (1) if they are primary gonococcal, (2) if smear or culture is positive with exacerbation or reinfection of old gonococcal infection, and (3) when the *Streptococcus hemolyticus* can be demonstrated as the infective agent.

Sulfanilamide should not be given in cases of cellulitis, pelvic or abdominopelvic abscess or to patients with acute exacerbations of chronic



pelvic infections with tuboovarian masses when the gonococcus cannot be demonstrated. Evidence accumulates that sulfanilamide should not be given to ambulatory patients.

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### THE SIGNIFICANCE OF THE TUBERCULIN TEST IN PREGNANCY\*

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IN THE midwestern part of this country, where our work was done, only about 25 per cent of the girls of college age have been infected with tubercle bacilli. At present the infection attack rate even in the cities is only approximately 1 per cent each year. Therefore, the girls attain the usual age of motherhood with 75 per cent or more free from tuberculous infection. To us the term "tuberculous infection" always means the presence of at least one primary tuberculosis complex, which consists of the primary lesion and those in the regional lymph nodes. Such lesions are usually small and rarely have they, per se, resulted in significant clinical tuberculosis.

On the basis of longitudinal studies of infected persons and on the basis of morbidity and mortality, it now appears that at least 25 per cent and probably more persons infected with tubercle bacilli have clinical manifestations of the disease at some subsequent time. In one group of children who reacted to tuberculin at the average age of eight years, it was found that by the time they had attained the average age of twenty-five years, 15 per cent had developed clinical tuberculosis.<sup>1</sup> (From 5 to 10 per cent of the deaths in this country are due to tuberculosis.) On the basis of results of extensive tuberculin testing of healthy appearing persons, it has been estimated that not more and probably less

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than 50 per cent of the population, including all ages, are infected with tubercle bacilli. Thus, 10 to 20 per cent of the infected die from this disease, and it becomes obvious that tuberculous infection is a serious matter.

The examination of the woman who presents herself for obstetric care should include the tuberculin test, just as certainly as it should include a test for syphilis. Since reactors to tuberculin have lesions of primary complexes, the physician should immediately examine such persons with the greatest of care for the presence of clinical tuberculosis.<sup>12</sup> If this disease happens to be in the lungs or kidneys, it usually is easily detected by x-ray, clinical and laboratory examination; if it be in the pelvic organs it may be more difficult of recognition unless it involves large areas. A single search for clinical tuberculosis in the pregnant woman does not suffice. Those who react to tuberculin may be entirely free from this form of the disease today, but it may make its appearance at any subsequent time.

The effect of pregnancy on tuberculosis has been extensively discussed in the literature.<sup>10</sup> Many views have been expressed by such workers as Dumarest,<sup>2</sup> Flick,<sup>4</sup> Jameson,<sup>8</sup> Jennings, Mariette, and Litzenberg,<sup>9</sup> and Rist.<sup>14</sup>

Much that has been said about tuberculosis and pregnancy has been based upon personal opinion rather than scientific observations. Thus, there is no incontrovertible evidence that pregnancy has any effect on tuberculous lesions of the primary complex, but it has been suggested that it does in some cases. Therefore, the pregnant women who react to tuberculin should be examined with extreme care.

The woman with a tuberculous focus, no matter how small and regardless of type, is not as good a risk as the woman who is entirely free from tuberculosis. This applies to any person regardless of pregnancy. Therefore, the physician can never determine with accuracy just when it is safe for a woman with a tuberculous lesion to become pregnant. It must always be a matter of opinion and judgment and each case must be decided upon its merits.

The treatment of pulmonary tuberculosis has advanced rapidly in the last few years and special methods have been devised for bringing the disease under control so that many women in whom termination of pregnancy might have been indicated in the past are now able to go through one or more pregnancies with no apparent effect on their tuberculosis. Collapse therapy has more value in tuberculosis therapeutics than all the other measures combined, and this is particularly true for the pregnant tuberculous woman. If progressive minimal or early, moderately advanced clinical tuberculosis is found after pregnancy occurs, immediate treatment, such as artificial pneumothorax, should be instituted. When the diseased area in the lung is collapsed, many women are able to continue with pregnancy with no deleterious results. Thus, from the standpoint of the health of the pregnant woman herself, it is of extreme importance that an adequate examination be made for tuberculosis. If the patient's disease is too advanced or the lung cannot be collapsed be-

cause of adhesions, strict bed rest, preferably in a hospital or a sanatorium, should be strongly recommended.

A tuberculous mother should be kept under close observation following delivery whether her disease is manifested only by a tuberculin reaction or whether definite clinical lesions can be located. If a tuberculin reaction only is present, x-ray films should be made every three to six months for a year, following which no year should be allowed to pass without a complete examination. If clinical lesions be present before delivery, active treatment should be continued as long as may be necessary. Those whose disease cannot be rendered non-contagious should be kept under strict isolation in a hospital or a sanatorium.

An equally important problem is the welfare of the infant. The source of tuberculous pneumonia, meningitis, and miliary disease in infants and small children who died is usually found to be contagious tuberculosis in the home or among relatives in close contact with the child. Often the infected contact had the disease in unsuspected form or was unaware of the danger of contagion.

Almost all tuberculous infants acquire the disease as a postnatal infection. The immediate removal of the newborn from the mother with contagious tuberculosis cannot be too strongly emphasized. If this is not done one must expect a high incidence of infection.

Most infants and children have but a few close adult contacts. It is usually only adults who have pulmonary tuberculosis in the contagious stage. The problem of preventing tuberculous infection is relatively simple and is a matter of recognizing and controlling the possible sources of infection.

The solution of the problem of tuberculosis in mother and infant begins with the examination of the pregnant woman for tuberculosis. These women readily submit to such examination because they are solicitous for the health of their offspring and themselves. This will reveal practically all primary tuberculosis complexes. Even though no clinical disease be present these are potential cases of clinical tuberculosis and they should know it. Those who have clinical lesions in the pre-symptom stage will be found and may be treated. Moreover, some would be found who already have the disease in the contagious stage. If they have advanced lesions, their infants may be protected against infection following delivery.

In April, 1934, a desperately ill infant of six months was admitted to the Minneapolis General Hospital. This infant had acute fatal tuberculosis. In seeking the source, the mother was found to have extensive tuberculosis, involving the left lung. Tubercle bacilli were abundantly present in her sputum. She had been in the General Hospital for delivery but no examination had been made for tuberculosis. This infant's infection should have been prevented. The treatment of the mother should have been instituted many months earlier than it was, although she was sent to a sanatorium as soon as she was recognized to be the source of her child's infection. She is still there and her condition appears hopeless. This case was brought to the attention of the late Dr. John Urner, who was chief of the Obstetrical Service of the

Minneapolis General Hospital. He immediately visualized the problem and made an arrangement whereby all the women who presented themselves for obstetric care in his out-patient department would be referred to our chest clinic. In 1934 the obstetric and tuberculosis divisions of the Minneapolis General Hospital organized a special clinic to assure careful study of patients presenting themselves for prenatal care. The following is a report of the procedure and experiences of the clinic since that time.

#### CLINICAL PROCEDURES

The procedure in the clinic consisted of administering 0.1 mg. of tuberculin intracutaneously to all patients. The usual second dose of 1.0 mg. was not used because of difficulty encountered in getting the patients to return at short intervals. It is strongly recommended when possible that the second dose be administered when there is no reaction to the first dose within seventy-two hours. Those who reacted to tuberculin were sent to the x-ray laboratory for a film of the chest. Reports of the findings were prepared by the roentgenologists, after which both the reports and the films were sent to our clinic. At the time the patient returned, regardless of the findings on the film, an opportunity presented itself to impress upon the expectant mothers the importance of creating conditions in the homes which would prevent their infants from developing contagious diseases, especially tuberculosis.

From June 1, 1934, to July 1, 1938, a total of 2,350 pregnant women were examined in our clinic. Of those, 1,491 did not react to tuberculin and 18 did not have the tests read (Table I). It is reasonably safe to conclude that the negative reactors had no tuberculosis problem at the moment. X-ray films were made of the chests of the 841 who reacted to tuberculin, but no evidence of disease was seen in 679 (Table I).

TABLE I. NUMBER RECEIVING TUBERCULIN TEST AND HAVING X-RAY FILM INSPECTION

Tuberculin reactors	841
Tuberculin non-reactors	1491
Tests not read	18
X-ray film examinations	841
No abnormal x-ray findings	679
Possible primary complex revealed by x-ray	135
Probable reinfection type lesions	26

These persons were informed that they had at least one primary tuberculosis complex, and although the lungs were clear to x-ray examination at that moment there was no guarantee that they would remain clear. It was explained that the examination was limited to the lungs because this is the most common site of the reinfection chronic form of tuberculosis. When the disease develops in the lungs it is likely to become contagious. They should therefore keep under observation not only through the present pregnancy but throughout life. Of the 841 tuberculin reactors, 135 had shadows on the x-ray film interpreted as representing deposits of calcium. The majority represented primary tuberculosis complexes. Those with such findings were given the same instructions as the tuberculin reactors who had clear chest films, since we recognized that this is a group who had had primary complexes of such size and so located that they could be visualized by this method, while the others had smaller or similar processes which were not visualized or were in other locations. Of the 841 tuberculin reactors, 26 (1.1 per cent) had shadows on the x-ray film which were thought to be due to chronic tuberculous lesions. Of these, 17 were classified as minimal, 4 as moderately advanced, and 5 as far advanced (Table II).

TABLE II. REINFECTION TYPE OF TUBERCULOSIS

Minimal	17
Moderately advanced	4
Far advanced	5
Total	26
Disease present on first examination	21
Disease appeared during pregnancy	2
Disease appeared subsequent to pregnancy	3
Extrapulmonary tuberculosis	
Renal with nephrectomy	1
Laryngitis	1
Enteritis	2
Peritonitis	1
Miliary	1
Treatment	
Sanatorium	9
Collapse therapy	4
Well-regulated life under close observation	13
Deaths	2

As helpful as the x-ray examination is in locating areas of disease, the findings on a single inspection can never constitute a diagnosis. For example, 2 of the women who reacted to tuberculin had shadows which were reported as tuberculosis, and cavity formation was mentioned. In each case the shadows completely disappeared within a month. These women had pneumonia which had not completely resolved when we first saw them, but the areas in which resolution was occurring were interpreted as cavities; therefore, whenever shadows were observed on the first x-ray film, we refrained from making definite diagnoses until adequate evidence was available.

A careful search, including cultures and animal inoculations, was made for tubercle bacilli in sputum when available. When this study began, we did not examine gastric washings of patients in whom bacilli could not be found by direct examination. However, we now strongly recommend this laboratory method. Serial x-ray films were made. When shadows persisted more than four to six weeks, we considered them due to tuberculosis, in spite of the possibility of error, since not all persistent shadows in adults are caused by this disease.

Some workers have used the fluoroscope as the first screen and x-ray films are made only of the chests of those persons who have definite or questionable shadows revealed on the screen. For example, Eisele and Mason<sup>3</sup> examined 4,040 apparently normal pregnant women in this manner and found 43 cases of previously unsuspected tuberculosis in 28 of whom the disease was progressive.

Ianne<sup>6</sup> used the tuberculin test and x-ray films of the reactors in the examination of 691 pregnant women, of whom 284 (41 plus per cent) reacted to tuberculin. Two hundred and fifty-two of the reactors were x-rayed. The x-ray revealed 12 cases of the reinfection type of disease. Of these, 10 were in the minimal, 1 in the moderately advanced, and 1 in the far-advanced stage of tuberculosis.

Hilleboe<sup>5</sup> has called attention to the work of G. Kjellin of Stockholm, Sweden, who has examined 100,00 pregnant women for tuberculosis and found 13 per cent with clinical tuberculosis. Thus, from available evidence it appears that slightly more than 1 per cent of pregnant women, who have been examined, have clinical tuberculosis requiring close observation or treatment.

#### COMMENTS

In 1937, there were born in the United States 2,203,337 infants. If 1 per cent of the mothers had clinical tuberculosis, more than 20,000 cases could have been discovered that year. It is doubtful whether more than a very small percentage of this number was actually dis-



covered, inasmuch as without modern methods of examination, including the tuberculin test and the x-ray film, only the more advanced cases with symptoms and abnormal physical signs come to light.

Thus, careful examinations of all pregnant women not only insure the finding of minimal tuberculous lesions, when treatment of the mother is of most avail, but also should prevent large numbers of infants from becoming infected and thus avoid the immediate and remote hazards.<sup>12</sup> This examination should extend to the adult members of the entire household, as well as nurses, physicians, and in fact, everyone who comes in contact with the infant. When this is done, the infant will be born in an environment free from contagious tuberculosis and meningitis, miliary tuberculosis, and tuberculous pneumonia, so fatal to infants, will become rarities.

Conservation was the keynote in the obstetric management of our patients. The conduct of labor was closely supervised with the purpose of conserving the mother's energy. Maternal exhaustion during labor was avoided. Great care was exercised toward making labor as short, quiet, and effortless as possible. This was accomplished by giving proper rest through the judicious and conservative use of analgesics and anesthesia and by seeing that the patient received proper nourishment during labor. Local anesthesia is preferred for surgical obstetric procedures. Prophylactic forceps delivery as soon as the cervix is completely dilated conserves the patient's energy by avoiding the expulsive effort during the second stage of labor. No cesarean sections were performed in our group.

#### CASE REPORTS

CASE 1.—L. B. In November, 1936, this woman of 22 years reacted to tuberculin, but the x-ray film of her chest revealed no evidence of disease. In February, 1937, she was admitted to the hospital as gravida i. The delivery was normal and the puerperium uneventful. In April, 1938, she was readmitted to the hospital and found to have bilateral pleurisy with effusion. Tuberculosis was strongly suspected, but smears made from the pleural fluid revealed no tubercle bacilli, and guinea pig inoculation was negative. At this time no evidence of disease could be seen in either lung on the x-ray film. Re-examination in July, 1938, revealed evidence of thickened pleura but the lung parenchyma was apparently clear. On Sept. 14, 1938, she was acutely ill and was readmitted to the hospital. At this time, the x-ray film examination of her chest revealed shadows suggestive of miliary tuberculosis. Guinea pig inoculation of sputum was later reported positive for tuberculosis. She delivered an eight-month, premature, living infant on Sept. 17, 1938, after labor of two and one-half hours. She had had no prenatal care. She died in September, 1938, and the post-mortem examination revealed miliary tuberculosis, tuberculous pneumonia, and tuberculous enteritis. This is a good example of a woman who had tuberculosis in November, 1936, as manifested by the tuberculin test but other phases of the examination, including the x-ray film of her chest, were not sufficiently delicate to determine its location.

CASE 2.—E. P. This woman, 32 years old, gravida i, was found to react to the tuberculin test in April, 1937. She was admitted to the Minneapolis General Hospital May 8, 1937, and delivered normally with episiotomy and repair. Following delivery her daily temperature varied from normal to 100° F. The x-ray film examination of her chest in May, 1937, revealed evidence of extensive disease in both lungs which proved to be due to tuberculosis. On May 19, 1937, she was discharged to a sanatorium. An attempt was made to institute artificial pneumothorax on the left side, but adhesions prevented a successful collapse. No

tubercle bacilli were found in her sputum and guinea pig inoculation from a specimen of stool was negative. Nevertheless, she had a diagnosis of tuberculous enteritis. In June, 1938, she left the institution against the advice of the medical staff. Although her condition was definitely improved by treatment, the staff considered her prognosis unfavorable. She was readmitted to the Minneapolis General Hospital on June 20, 1938, with intestinal hemorrhage and died the same day. Here we have a case of extensive pulmonary tuberculosis which was only first suspected and discovered through the use of the tuberculin test during pregnancy.

CASE 3.—E. R., 23 years old, gravida iv, para iii, was admitted to the hospital in November, 1937. Her pregnancy was at term, and she delivered normally with episiotomy and repair. The puerperium was uneventful and she left the hospital on the ninth day. In November, 1937, she reacted to tuberculin, but a physical and fluoroscopic examination of her chest revealed no evidence of disease. However, in April, 1938, an x-ray film examination revealed evidence of minimal disease in the left lung. No tubercle bacilli could be found in her sputum. In December, 1938, she was admitted to a sanatorium with far-advanced pulmonary tuberculosis, with cavitation in the left lung. She also had tuberculous laryngitis. At this time tubercle bacilli were found in her sputum. Artificial pneumothorax was attempted but adhesions prevented a satisfactory collapse. Intrapleural pneumolysis was done in February, 1939. She is still in the sanatorium and her prognosis is now thought to be favorable. This case illustrates the fact that the tuberculin test is superior to the physical and fluoroscopic examination in determining the presence of tuberculosis. It is possible that an x-ray film of her chest might have revealed evidence of disease in November, 1937. Again, the lesion may have been so small at that time that it escaped detection. Nevertheless, the film should have been made, as it is far superior to physical examination and to the usual fluoroscopic examination.

CASE 4.—D. H. In March, 1936, this woman of 29 years reacted to the tuberculin test. The x-ray film examination of her chest revealed evidence of a small lesion in the left upper lung field. She was admitted to a sanatorium in May, 1936, where the x-ray film revealed no change in the shadow seen in March. In July, 1936, as gravida iii, para ii, she delivered a full-term infant at the sanatorium. During her stay in the sanatorium, tubercle bacilli were not found in her sputum. However, tuberculosis of the left kidney was diagnosed and tubercle bacilli were recovered from a specimen of urine from the left ureter. She left the sanatorium against the advice of the medical staff in August, 1937, at which time the disease in the left upper lobe had decreased considerably. On October, 1937, she was readmitted to the sanatorium and nephrectomy was performed. Miliary tuberculosis was found in the left renal pelvis and ureter. No tubercle bacilli have been found in her sputum. The pulmonary lesion remained unchanged. She was discharged from the sanatorium with four hours exercise in November, 1938. This case demonstrates the fact that tuberculous lesions may be multiple and, therefore, the examination of the chest alone does not always suffice. Clinical lesions may be present in other parts of the body. Here the pulmonary lesion was apparently stationary while the renal lesion was progressive.

#### CONCLUSIONS

1. The woman who enters upon the period of pregnancy with a tuberculin reaction is not as good a risk as the woman who is a non-reactor, since the tuberculin reaction indicates the presence of living tubercle bacilli in the body.
2. Routine tuberculin tests followed by x-ray films of the chests and complete examinations of the reactors as indicated should rank with routine Wassermann tests and complete examinations of the reactors as a medical necessity in pregnant women.

3. The pregnant woman with tuberculosis should receive whatever treatment is indicated throughout the period of pregnancy and for as long thereafter as necessary. Collapse therapy is valuable when indicated.

4. The offspring of mothers with tuberculosis should have no contact with the mother as long as her disease is contagious.

5. Tuberculous foci may appear or extend during or following pregnancy.

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520 LA SALLE BUILDING.

## PREMATURE ELECTIVE RUPTURE OF THE MEMBRANES

### A COMPARATIVE STUDY

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IN 1936, Plass and Seibert<sup>1</sup> reported on the results obtained in 681 consecutive patients in whom premature rupture of the membranes had been employed as a means for inducing labor, and concluded that this procedure offers the safest and most efficient method for inaugurating parturition. Since the series included 84 patients who presented some complication of pregnancy and since no control material was utilized, the data did not permit a real comparison except in most general terms. Because of the apparent good results, and because of the peculiar conditions in regard to obstetric patients in the University Hospitals, elective premature rupture of the membranes has been employed extensively during the intervening period. The present study was designed to permit an accurate comparison between patients who had late spontaneous rupture of the membranes and those who were subjected to induction of labor by elective early rupture of the bag of waters.

#### MATERIAL

One thousand consecutive normal parturient women with cephalic presentations and with later spontaneous rupture of the membranes constitute Group I; while a similar number of normal women in whom labor was induced by early elective rupture of the membranes constitute

Group II. Cephalopelvic disproportion and abnormal presentations were again recognized as contraindications to artificial rupture. Breech and transverse presentations were excluded from the analysis, since by selection they would all fall in Group I and might affect the results.

Group I included 308 primigravidas and 692 multigravidas; while in Group II the corresponding figures were 281 primigravidas and 719 multigravidas. There were 47 patients with minor degrees of pelvic contraction (simple flat, 10; generally contracted, 11; and funnel, 26), in none of whom was there any evidence of disproportion. The recorded presentations as shown in Table I indicate an unusual percentage of occiput anteriors, but the distribution between right and left occiput positions seems reasonably accurate.

*Analgesia and Anesthesia.*—Some form of sedation was given during labor to 307 individuals in Group I (morphine and scopolamine, 176; morphine, 26; various barbituric acid derivatives, 74; pentobarbital and scopolamine, 24; and rectal ether, 7); and to 364 patients in Group II (morphine and scopolamine, 255; morphine, 27; various barbituric acid derivatives, 55; pentobarbital and scopolamine, 16; rectal ether, 11). In the remaining 1,329 cases, mostly multigravidas, no sedative drugs were administered.

TABLE I. ANALYSIS OF CEPHALIC POSITIONS IN THE TWO GROUPS

	NO DATA	L.O.A.	L.O.T.	L.O.P.	R.O.A.	R.O.T.	R.O.P.	BROW	FACE
Group I (Spontaneous)	8	499	34	21	354	36	43	2	3
Group II (Elective)	3	494	77	23	315	48	38	1	1

Some form of anesthesia was given to 1,881 individuals during the second stage, usually as the head was coming over the perineum; in the remaining 115 patients, delivery was too rapid to permit anesthetization. In four instances there were no data. Ethylene was used alone in 1,716 cases, and with ether in 47; nitrous oxide was given to 19 patients, open ether to 31, chloroform to 34, cyclopropane to 2, and local infiltration was employed 32 times. The distribution was approximately the same in the two groups and is probably without any real significance in relation to the factors studied.

TABLE II. COMPLICATIONS OF LABOR

	GROUP I (SPONTANEOUS)	GROUP II (ELECTIVE)
Complications absent	930	930
Complications present	70	70
Intrapartum infection	13	25
Post-partum hemorrhage	46	34
Retained placenta	3	2
Prolapse of cord	2	4
Maternal exhaustion	5	1
Prolapse of arm	1	4

*Complications of Labor.*—Table II enumerates the various complications of labor, other than the prolongation of parturition beyond thirty hours, in the two groups. It will be noted especially that intrapartum infection was approximately twice as frequent in Group II as in Group I, presumably because long latent periods predispose to uterine infection before delivery. On the other hand, there were 50 per cent more post-partum hemorrhages in Group I than in Group II, a fact for which

there is no obvious explanation. Prolapse of the cord occurred twice in Group I and four times in Group II, but both babies in the former were lost (100 per cent) whereas there was only one fetal fatality (25 per cent) in the latter. The only maternal death involved a patient in Group I who developed agranulocytosis following arsphenamine therapy for latent syphilis.

*Special Data on Group II.*—The technique of rupturing the membranes was that previously described<sup>1</sup> except that a small amount of aqueous merthiolate (1:1000) or of mercuric iodine (1:1000) was introduced into the vagina prior to puncture of the bag of waters. No particular effort was made to "strip" the membranes during the procedure. Except in 14 instances, the rupture of the membranes was preceded by medical induction (the Watson technique was employed in 978 patients, and 8 others were given only castor oil and quinine). In certain cases of prolonged latent periods various forms of medication were administered in an attempt to stimulate uterine contractions (castor oil and pituitrin, 1; castor oil and quinine, 2; quinine, 5; quinine and pituitrin, 1; pituitrin, 7; and hot soapsuds enema, 1).

TABLE III. HEIGHT OF PRESENTING PART AT TIME OF ELECTIVE RUPTURE

Floating	27
Fixed above spines	805
Engaged, at spines	134
Engaged, below spines	6
No data	28
Total	1000

The station of the presenting part at the time of elective rupture is presented in Table III. It should be noted that the head was fixed but not engaged in the majority of instances, but was floating in only 27 cases. Effacement of the cervix was complete in 117 cases and partial in 235, while in 618 patients there was no retraction (there were no data on 30 cases). The external os was closed in 15 cases, but was dilated 1 to 2 cm. in 663 and open 2 to 5 cm. in 284 cases (there were no data on 38 patients). In general it is unwise to attempt puncture of the bag of waters when the cervix will not easily admit one finger (1 to 2 cm.).

#### MATERNAL RESULTS

The available data were analyzed in conformity with the plan employed in the early paper, since it is felt that the factors there considered are perhaps most important in any attempted evaluation. Information on the relative condition of the cervix after spontaneous and elective membrane rupture was not available because of the impossibility of carrying out follow-up examinations on a clientele which came from all parts of the State. However, the experience gained from routine speculum examinations at the time of discharge from the hospital (eight to ten days after delivery) tends to confirm the observations of others (Schumann<sup>2</sup>) that "dry labor" does not increase the number or severity of cervical lacerations.

*Latent Period.*—The period elapsing between the rupture of the membranes and the onset of active, strong labor pains was less than one hour in 615 patients, in many of whom preliminary pains had already appeared as a result of the medical induction. In 224 women, the latent period was one to six hours, in 104 it was six to twenty-four hours, and in 39, there was a delay of more than twenty-four hours (no data are available in 18 instances) (Table IV). The longest latent period, 136 hours, was followed by normal delivery and an afebrile puerperium. In approximately 14 per cent of the patients the latent period was longer than six hours; parity appears to have no particular significance except in the group with six or more previous children, where the percentage is increased by one-half to 21 per cent.



TABLE IV. THE RELATION OF PARITY TO THE LATENT PERIOD

NUMBER OF PREVIOUS CHILDREN	TOTAL CASES	NO DATA	LABOR LESS THAN ONE HOUR	LATENT PERIOD LABOR 24 HR. AND UP			
				1 TO 5	6 TO 23	NUMBER	PER CENT
0	281	7	161	75	28	10	3.5
1	215	4	131	50	24	6	2.8
2	155	3	97	36	13	6	3.9
3 to 5	237	4	155	46	23	9	3.8
6 or more	112	0	71	17	16	8	7.1
No data	--	--	--	--	--	--	--
Total	1,000	18	615	224	104	39	3.9

The condition of the cervix at the time of rupture of the membranes apparently had a definite effect upon the length of the latent period, as might have been anticipated. Noneffacement of the canal and the absence of preliminary dilatation of the os both predisposed to prolongation of the latent period, but did not invariably postpone the onset of labor. In 59 per cent of the women with uneffaced cervixes and in 60 per cent of those in whom the os was dilated only to admit one finger (not more than 2 cm.), the latent period was less than one hour. On the other hand, 80 per cent of those with latent periods of twenty-four hours or more had uneffaced and undilated cervixes.

The duration of the pregnancy as evidenced by the size of the baby evidently influenced the latent period more than any other factor. Among the 39 women with latent periods of more than twenty-four hours, there were five children (12.8 per cent) weighing less than 2,500 Gm., whereas children of this size represented only 1.8 per cent of those born to mothers having latent periods of under one hour. This relationship was more strikingly shown in a separate series of 130 patients in whom labor was induced by this technique, because of medical indications, and among whom there were 8 latent periods of more than twenty-four hours; three of these children weighed less than 2,500 Gm. (37.5 per cent).

TABLE V. DURATION OF LABOR IN RELATION TO PARITY

GROUP	PARITY	TOTAL IN GROUP	DURATION OF LABOR						
			0-3 HOURS	3-5 HOURS	6-11 HOURS	12-17 HOURS	18-29 HOURS	MORE THAN 30 HOURS	
								NO. CASES	PER CENT
Spontaneous	0	308	10	38	117	82	48	13	4.2
Elective		281	8	39	121	70	30	13	4.6
Spontaneous	i	213	22	55	85	40	9	2	0.9
Elective		215	28	74	70	26	12	5	2.3
Spontaneous	ii	156	24	49	45	21	16	1	0.6
Elective		155	22	54	52	18	4	5	3.2
Spontaneous	iii to v	217	41	63	68	24	16	5	2.3
Elective		237	38	74	78	26	12	9	3.8
Spontaneous	vi and more	106	20	23	39	13	9	2	1.9
Elective		112	19	32	32	14	7	8	7.1
Spontaneous	Total	1000	117	228	354	180	98	23	2.3
Elective	Total	1000	115	273	353	154	65	40	4.0

*Duration of Labor.*—The total duration of labor (Table V) shows no significant difference in the two groups, except that there was a definite increase in the number of prolonged parturitions (more than thirty hours) among the parous women in Group II. The percentages of prolonged labors in the primigravidas (4.2 per cent and 4.6 per cent, respectively) were practically identical; but in each division of the multigravidas the percentage was appreciably higher, with the difference most

marked in those with the greatest number (six or more) of previous children. On the other hand, labors of less than twelve hours' duration were slightly less common (77.5 per cent) in Group I than in Group II (79.3 per cent). Such data suggest that the birth process tends to be either slightly shortened or somewhat prolonged when labor is induced electively by premature rupture of the membranes, but give no clue as to the factors producing either tendency.

*Method of Delivery.*—Parturition was spontaneous in 93 per cent of each group, with operative intervention undertaken only for definite indications in the remaining 7 per cent. Among the primigravidas, the operative incidence was above the average, with 15.9 per cent in Group I and 20.3 per cent in Group II. The incidence of the various types of operations is specified in Table X.

*Blood Loss.*—The average blood loss was 164 c.c. in Group I and 201 c.c. in Group II, but there were more patients (46) in the former group who suffered more or less severe post-partum hemorrhage (more than 600 c.c. blood loss) as against 34 in the latter. This higher incidence of excessive bleeding among the Group I patients was apparent irrespective of the duration of labor (Table VI), and became increasingly noticeable as the length of parturition increased.

TABLE VI. BLOOD LOSS IN RELATION TO LABOR

GROUP	DURATION OF LABOR	TOTAL IN GROUP	BLOOD LOSS			
			LESS THAN 199 C.C.	200 TO 599 C.C.	600 C.C. OR MORE	
					NO. CASES	PER CENT
Spontaneous	0 to 5	345	198	133	14	4.0
Elective	hours	388	216	161	11	3.8
Spontaneous	6 to 17	534	253	259	22	4.3
Elective	hours	507	246	241	20	3.9
Spontaneous	More than	121	49	62	10	8.2
Elective	18 hours	105	51	51	3	2.8
Spontaneous	Total	1000	500	454	46	4.6
Elective		1000	513	453	34	3.4

TABLE VII. BLOOD LOSS IN RELATION TO LATENT PERIOD\*

GROUP	LATENT PERIOD	TOTAL GROUP	BLOOD LOSS			
			LESS THAN 199 C.C.	200 TO 599 C.C.	600 C.C. OR MORE	
					NO. CASES	PER CENT
Elective	0 to 1 hour	615	314	279	22	3.6
Elective	1 to 6 hours	224	114	106	4	1.8
Elective	6 to 24 hours	104	61	38	5	4.7
Elective	More than 24 hours	39	18	19	2	5.1
Elective	Total	982	507	442	33	3.4

\*No data on latent period in 18 cases.

Prolongation of the latent period in Group II produced some increase in the number of post-partum hemorrhages (Table VII) among those who did not respond within one hour. The lower incidence when the latent period was from one to six hours may well be an artifact dependent upon unknown factors.

*Puerperal Morbidity.*—The puerperal morbidity rates based upon readings of 100.4° F. or more at any time during the first ten days of the puerperium with temperatures taken every four hours day and night were 25.0 per cent for Group I and 25.4 per cent for Group II (Table VIII). One day fevers were present in 141

TABLE VIII. POST-PARTUM FEVER IN RELATION TO PARITY, LATENT PERIOD, AND DURATION OF LABOR

GROUP	HIGHEST POST-PARTUM TEMPERATURE	PARITY		DURATION OF LABOR			LATENT PERIOD*	
		NONE	1 OR MORE	0 TO 17 HOURS		18 HOURS OR MORE	0 TO 5 HOURS	6 OR MORE HOURS
Spontaneous	Under 100.4° F.	196 63.6%	554 80.0%	669 76.1%	81 66.9%			
Elective		177 63.0%	569 79.9%	681 76.1%	65 61.9%		627 74.7%	99 70.0%
Spontaneous	100.4° F.	112 36.4%	138 20.0%	210 23.9%	40 33.1%			
Elective	or more	104 37.0%	150 20.1%	214 23.9%	40 38.1%		212 25.3%	42 30.0%
Total								
Spontaneous		308	692	879	121			
Elective		281	719	895	105		839	141

\*No data on 20 cases.

TABLE IX. FATE OF CHILD IN RELATION TO WEIGHT

BIRTH WEIGHT (GRAMS)	GROUP	TOTAL BIRTHS	STILLBIRTHS						NEONATAL DEATHS							
			INTRA-PARTUM INFECTION	HYDRO-CEPHALIC	ANCE-PHALIC	CON-GENI-TAL SYPH-ILIS	INTRA-CRA-NIAL HEMOR-RHAGE	PREMA-TURITY ATELEC-TASIS AS-PHYX-IA	PRO-LAPSED CORD AND ARM	NO DATA	MAL-FOR-MATIONS	PNEU-MONIA	ANCE-PHALIC	PREMA-TURITY ATELEC-TASIS AS-PHYX-IA	INTRA-CRA-NIAL HEMOR-RHAGE	
Up to 2,500	Spontaneous	51			1	1	1*	1		1	1			5	0	3*
	Elective	20			2					0				1		
Above 2,500	Spontaneous	949			1		2	1	2	0	1	2		1	0	2†
	Elective	980	2	1			3		1	2				2	1	
Totals	Spontaneous	1000	2	2	2	1	3	2	2	1	1	2	0	6	0	3
	Elective	1000		1	2	0	3	0	1	2	1	0	0	3	1	2

\*Cisternal puncture.

†Clinical diagnosis.

patients in Group I, leaving a true morbidity rate of 10.9 per cent, and in 120 patients in Group II, making an actual morbidity rate of 13.4 per cent. Twelve patients (1.2 per cent) in Group I and 15 (1.5 per cent) in Group II had fevers which persisted for seven days or longer. None of the infections threatened life and there was only one death in the 2,000 cases, as already mentioned. Primiparity, prolongation of the latent period, and prolonged labor were associated with definite increase in the incidence of febrile reactions.

*Fetal Results.*—There were 13 (1.3 per cent) stillbirths and 12 (1.2 per cent) neonatal deaths, for a total fetal mortality of 2.5 per cent in Group I, as against 11 (1.1 per cent) stillbirths and 7 (0.7 per cent) neonatal deaths for a total fetal loss of 1.8 per cent in Group II (Table IX). Such data, however, offer an inaccurate means of comparison, since Group I contained 51 babies weighing less than 2,500 Gm., whereas there were only 20 such premature infants in Group II, where every effort was made to insure the maturity of the child before proceeding to the induction. There were 5 stillbirths and 9 neonatal deaths among the prematures in Group I, a total mortality of 27.4 per cent, as against 2 stillbirths and 1 neonatal death among the premature children in Group II, a total loss of 15 per cent.

Considering only the mature infants, there was a mortality rate of 1.1 per cent in Group I and of 1.5 per cent in Group II, the difference being largely explained by the higher incidence (5 to 2) of intracranial hemorrhage and the lower frequency of congenital malformation (2 to 3) in Group II as compared with Group I.

In Group I there were two cases of prolapsed cord, both in vertex presentations, when delivery was effected by midforceps and resulted in stillborn children. One prolapsed arm was treated without radical intervention and the child survived. Group II showed four prolapsed cords and an equal number of prolapsed arms. Two patients with funic prolapse were delivered by podalic version and extraction and 2 by forceps; the single fetal death occurred during forceps delivery. Among the 4 prolapsed arms, 2 were delivered by version and extraction, 1 by forceps and 1 spontaneously. The lone fatality occurred in 1 of the patients delivered by version. In each group, there were 2 fetal deaths associated with prolapse of the cord or an extremity, even though these complications were almost three times as common in patients subjected to elective rupture of the membranes.

In Group II, the fetal risk increased from 0.8 per cent (5 among 615) in those with a latent period of less than one hour to 11.3 per cent (4 among 39) when the onset of labor was delayed more than twenty-four hours.

In both groups, prolongation of the birth process was associated with an increased fetal fatality rate. When delivery occurred within six hours of the onset of labor, the mortality rates were 2.0 per cent in Group I and 0.8 per cent in Group II; with labors lasting six to eighteen hours, the values were 3.1 per cent and 1.9 per cent; and when delivery occurred only after more than eighteen hours, the rates were 5.0 and 5.8 per cent, respectively.

Among primigravidas the fetal loss was higher (Group I, 3.9 per cent; Group II, 2.1 per cent) than in those women who had previously borne one or more children (Group I, 1.9 per cent; Group II, 1.7 per cent).

TABLE X. METHOD OF DELIVERY IN RELATION TO FATE OF CHILD

METHOD OF DELIVERY	DISCHARGED ALIVE	STILLBIRTHS	NEONATAL DEATHS	TOTALS
Series I				
Spontaneous	912	9	9	930
Low forceps	58	0	3	61
Midforceps	4	2	0	6
Version	1	1	0	2
Craniotomy	0	1	0	1
Series II				
Spontaneous	915	9	7	931
Low forceps	58	1	0	59
Midforceps	5	1	0	6
Version	3	1	0	4

## DISCUSSION

The results obtained in this series of 1000 inductions of labor by premature artificial rupture of the membranes largely confirm our previous conclusion that this procedure is both efficient and relatively safe, but comparison with an equal number of uninduced labors does not lend support to the belief that labors induced in this fashion differ materially from those which start spontaneously. Certain apparent advantages gained under this type of induced labor are counterbalanced by other evident risks which appear to be connected directly with the technique employed.

Intrapartum infections and prolapses of the cord and arm were twice as frequent in the induced series, and this increase may probably be attributed directly to the procedure. On the other hand the reduced number of post-partum hemorrhages in Group II can scarcely be ascribed to any protective action of the induction technique, since the average blood loss among the entire group of patients was somewhat greater than in Group I and was increased by extension of the latent period beyond six hours.

The effect of early membrane rupture on the duration of labor is not clear-cut and the statistical results are hard to interpret, since there seems to be a tendency both toward shorter average labors and for an increase in the number of unusually prolonged parturitions. Among the primigravidas, the total duration of labor was less than twelve hours in 53.6 and in 59.8 per cent, respectively, in Groups I and II, but there was a slightly higher percentage of prolonged labors (4.6 per cent) in Group II than in Group I. On the other hand, 77.2 per cent and 79.7 per cent of the multigravidous labors were completed in less than twelve hours in Group I and II, respectively; whereas labors of more than thirty hours' duration were more than two and one-half times as common (3.7 per cent) in Group II as in Group I (1.4 per cent), a fact which does not correlate with the lower incidence of post-partum hemorrhage in the former.

The fact that 25 per cent of the patients in each group had post-partum temperature elevations to 100.4° F. or above may seem excessive, but it must be recalled that temperatures were taken every four hours day and night and that one-half to two-thirds of these fevers were without clinical significance, in that they disappeared spontaneously in less than twenty-four hours. The incidence of true puerperal morbidity, as represented by the presence of fever for more than one day, was slightly higher in the induced series, and may be explained by the inevitable vaginal manipulations. There were, however, no serious infections and persistent fevers were practically as common in one group as in the other.

The lower fetal death rate in the induced group has already been explained on the basis of the smaller number of premature infants incident to the method of selecting patients for induction. It is interesting that only one infant was lost because of prolapsed cord in Group II as against two in Group I; obviously this is merely a coincidence. The data suggest that intracranial hemorrhage is less frequent among mature infants when the membranes are allowed to rupture spontaneously, but



the size of the series does not permit such a conclusion, since several of the children were not subjected to autopsy.

#### CONCLUSIONS

The induction of labor by premature artificial rupture of the membranes does not significantly alter the birth process or affect the prognosis for the mother or her child.

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### CORRELATION OF FRIEDMAN TEST AND PHASE OF ENDOMETRIUM IN ECTOPIC PREGNANCY

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THE diagnosis of a recently ruptured ectopic gestation with profuse intra-abdominal hemorrhage is usually not difficult. It is the unruptured extrauterine pregnancy or one with slight or recurrent internal bleeding that taxes one's diagnostic acumen. Here the history, physical examination, and routine laboratory procedures are frequently inadequate to establish the diagnosis. These findings must often be supplemented by the Aschheim-Zondek test (or Friedman modification), uterine curettage, peritoneoscopy, cul-de-sac aspiration, posterior colpotomy, and occasionally an exploratory laparotomy. One should resort to any feasible and practical test or procedure in order to avoid an unnecessary abdominal operation. With these facts in mind, the writers believed that it would be of value to study the type of endometrium, the result of the Friedman test, the condition of the placental tissue of the excised salpinx, and the correlation of the data thus obtained with the clinical picture.

For the purpose of this study, the cases of patients with ectopic pregnancy entering the Gynecologic Service of the Bellevue Hospital from June, 1934, to December, 1939, inclusive, were reviewed. At Bellevue Hospital extrauterine pregnancy is not an uncommon finding, and during this five-and-one-half-year period there were 193 such diagnoses, confirmed by operation. Because, however, many of these patients presented the picture of hemorrhagic shock and required as short a surgical procedure as possible, and because curettage as a diagnostic aid in ectopic pregnancy was seldom used until relatively recently, all the desired data could be secured on only 32 patients. It is from these 32 cases with complete data that our information was obtained (see Table II).

Siddall and Jarvis in a review of 38 cases from the Harper Hospital at Detroit concluded that uterine curettage is very valuable as a diagnostic aid in ectopic

gestation. They state that "it is not an unduly dangerous procedure," and that "the finding of intact decidua without chorionic villi is strong presumptive evidence of extrauterine pregnancy. The absence of decidual reaction is not reliable evidence against ectopic pregnancy." They found, as did others before them, that the presence or absence of decidua is determined by the duration of the uterine bleeding. In our series we find that not only the duration, but also the amount of bleeding, is an important factor.

Siddall and Jarvis charted the relationship of the duration of the bleeding to the presence or absence of decidua, and they collected other reports from the literature. In Table I we have added our own findings to those charted by Siddall and Jarvis. Judging by the small number of cases reported, curettage is not frequently employed in ectopic pregnancy. Siddall found uterine decidua in every case in which the bleeding, irrespective of the amount, lasted ten days or less. In our series of 32 cases there are 5 patients that bled ten days or less (including 2 who had no history of bleeding), and all 5 showed decidua in the uterus. Three patients bled for two weeks, and two of these showed decidua.

TABLE I. SIX SERIES OF EXTRAUTERINE PREGNANCIES SHOWING INCIDENCE OF DECIDUA ACCORDING TO ONSET OF ABNORMAL BLEEDING BEFORE ENDOMETRIUM WAS OBTAINED (ADAPTED FROM SIDDALL AND JARVIS)

ONSET OF ABNORMAL BLEEDING BEFORE SPECIMEN WAS SECURED	SERIES	CASES	DECIDUA	PERCENTAGE
None to one week	Sampson	2	2	100.0
	Geist and Matus	11	10	90.9
	Moritz and Douglas	12	2	16.7
	Boerner	11	10	90.9
	Siddall and Jarvis	7	7	100.0
	Bellevue Hospital	4	4	100.0
	Total	47	35	74.5
Eight days to two weeks	Sampson	3	1	33.3
	Geist and Matus	12	7	58.3
	Moritz and Douglas	11	2	18.2
	Boerner	4	1	25.0
	Siddall and Jarvis	8	6	75.0
	Bellevue Hospital	4	3	75.0
	Total	42	20	47.6
Fifteen days to three weeks	Sampson	1	0	00.0
	Geist and Matus	6	2	33.3
	Moritz and Douglas	6	1	16.7
	Boerner	7	2	28.6
	Siddall and Jarvis	3	2	66.7
	Bellevue Hospital	5	4	80.0
	Total	28	11	39.3
Twenty-two days to four weeks	Sampson	8	2	25.0
	Geist and Matus	4	2	50.0
	Moritz and Douglas	12	1	8.3
	Boerner	4	1	25.0
	Siddall and Jarvis	8	3	37.5
	Bellevue Hospital	6	0	00.0
	Total	42	9	21.4
Twenty-nine days to twelve weeks	Sampson	11	0	00.0
	Geist and Matus	6	2	33.3
	Moritz and Douglas	12	2	16.7
	Boerner	4	0	00.0
	Siddall and Jarvis	12	4	33.3
	Bellevue Hospital	13	3	23.1
	Total	58	11	18.9
	All cases	217	86	39.6

Thus, of 8 cases that bled two weeks or less, 7 (85 per cent) had uterine decidua. Five patients bled from two to three weeks, and 4 (80 per cent) showed decidua. Of 6 patients that bled three to four weeks none showed decidua, but of 19 patients who bled four to twelve weeks, inclusive, 3 (16 per cent) contained decidua. Expressing these facts in another way, of 13 patients who bled three weeks or less, 11 (85 per cent) showed decidua, and of 19 patients who bled from twenty-two days to twelve weeks, only 3 (16 per cent) had decidua.

Of the 32 cases studied, 14 had decidua. Of the 14 with decidua all bled only scantily or not at all, except for one. This one bled moderately for three weeks. Another patient, however, bled scantily for twelve weeks, and the uterus still contained decidua. No other patient of the 32 bled this long. Hence, it immediately appears that the amount of uterine bleeding, as well as the duration, is important in predicting the presence or absence of uterine decidua in ectopic pregnancy.

For the purpose of this paper, the amount of bleeding was described as scanty (including spotting), moderate, or profuse. Naturally, these terms are relative, but they were charted before the study of the endometrium was made and were never again seen until this paper was in preparation, so that the authors could

TABLE II. BELLEVUE HOSPITAL CASES OF ECTOPIC PREGNANCY SHOWING RELATIONSHIP BETWEEN DURATION AND AMOUNT OF VAGINAL BLEEDING, TYPE OF ENDOMETRIUM, RESULT OF FRIEDMAN TEST AND DEGREE OF DEGENERATION OF PLACENTAL TISSUE

NO.	LAST MENSTRUAL PERIOD. WEEKS BEFORE SPECIMEN WAS OBTAINED	ONSET OF VAGINAL BLEEDING. WEEKS BEFORE SPECIMEN WAS OBTAINED	TYPE OF BLEEDING. SCANT, MODERATE OR PROFUSE	ENDOMETRIUM. PHASE	FRIEDMAN TEST RESULT	PLACENTAL TISSUE. DEGREE OF DEGENERATION
1	13	0	0	Decidua	Positive	Slight
2	9	0	0	Decidua	Positive	None
3	5	$\frac{1}{2}$	Scant	Decidua	Positive	Slight
4	8	$\frac{2}{7}$	Scant	Decidua	Positive	Slight
5	8	$1\frac{1}{2}$	Scant	Decidua	Positive	None
6	6	2	Scant	Decidua	Positive	Slight
7	3	2	Scant	Decidua	Positive	Slight
8	4	3	Scant	Decidua	Positive	None
9	8	3	Scant	Decidua	Positive	Slight
10	13	3	Moderate	Decidua	Positive	Insufficient
11	11	3	Profuse	Decidua	Positive	Slight
12	11	6	Scant	Decidua	Positive	Slight
13	8	8	Scant	Decidua	Positive	None
14	12	12	Scant	Decidua	Positive	Slight
15	8	2	Scant	Proliferating	Positive	Slight
16	3	3	Moderate	Proliferating	Positive	None
17	4	4	Moderate	Proliferating	Negative	Slight
18	8	4	Moderate	Proliferating	Positive	Slight
19	8	4	Moderate	Proliferating	Positive	Slight
20	9	4	Moderate	Proliferating	Positive	None
21	11	4	Profuse	Proliferating	Negative	Moderate
22	7	5	Scant	Proliferating	Positive	Slight
23	6	6	Scant	Proliferating	Negative	Moderate
24	7	7	Scant	Proliferating	Positive	None
25	13	7	Moderate	Proliferating	Positive	Marked
26	13	8	Moderate	Proliferating	Positive	Moderate
27	9	9	Scant	Proliferating	Negative	Marked
28	13	10	Moderate	Proliferating	Negative	Marked
29	8	4	Scant	Secretory	Positive	Slight
30	9	6	Scant	Secretory	Negative	Moderate
31	10	6	Moderate	Secretory	Negative	Marked
32	10	6	Moderate	Secretory	Negative	Marked

not be influenced in the use of terms. Two patients had no history of bleeding, 17 bled scantily, and 13 bled moderately or profusely. Both of those with no bleeding had decidua. The 17 with scanty bleeding bled from one day to twelve weeks, and 12 (63 per cent) of these had decidua; adding the two with no bleeding to this series, 14 of the 19 patients (74 per cent) with scanty or no bleeding, irrespective of the duration of the bleeding, had decidua. The 13 patients with moderate or profuse bleeding bled from two to ten weeks, and only 2 (15 per cent) had decidua. Of these two, one bled moderately for three weeks and one profusely for three weeks, both thus bleeding a relatively short period of time.

As mentioned earlier, of 19 patients that bled longer than three weeks, only 3 had decidua. In all three the bleeding was only scanty in amount (see Table II). Hence, no patient who bled more than scantily for more than a period of three weeks still showed decidua. It appears therefore that any patient with an ectopic pregnancy who bleeds only scantily, regardless of the duration of the bleeding, may still have decidua, but with a decreased expectancy for decidua, as the duration of the bleeding increases; and that any patient who bleeds moderately or profusely for more than three weeks is extremely likely not to have decidua. The expectancy of decidua appears to be inversely proportional to the total amount of blood lost per vaginam, the less the blood loss, the greater the chance for decidua being present. Consequently, a patient that bleeds scantily for a certain duration of time is much more likely to have decidua than is the patient who bleeds moderately or profusely for the same period of time.

Of the 32 ectopic pregnancies studied, 24 had a positive and 8 a negative Friedman test. No patient with a negative Friedman test had decidua. No patient with decidua had a negative Friedman test. While the presence of decidua required a positive Friedman reaction in every case, a positive Friedman test did not guarantee the presence of decidua. Of the 24 patients with positive Friedman, 14 had decidua and 10 did not. According to an earlier conclusion, in the 10 cases without decidua one would expect either a long period of scanty or more bleeding, or a relatively short period with moderate or profuse bleeding. This is true except for one patient who bled for two weeks and only scantily (Case 15 of Table II); of the remaining 9 patients without decidua, 8 bled four weeks or longer, and one bled moderately for three weeks. Here again one sees the importance of the amount as well as the duration of bleeding in predicting the presence or absence of uterine decidua.

An attempt was made, by microscopic examination of the Fallopian tube, to correlate the state of degeneration or preservation of the placental tissue in the tube with the actual Friedman test. The authors do not agree with Kaplun, who states that there is no parallelism between the morphologic activity of the trophoblast and the outcome of the Aschheim-Zondek reaction. For the purpose of this study, the placental tissue was graded according to its degree of degeneration as 0, slight, moderate, and marked degeneration (see Table II). The actual result of the Friedman test was not known at the time of the grading of the degree of degeneration and the recording of the probable result of the rabbit test.

In the cases designated a 0 placental degeneration, the placental tissue was in perfect condition; the villi showed no fibrosis, and they contained blood vessels which contained erythrocytes. In these patients it was felt that the Friedman test should be positive. There were 7 such patients. In all 7 the actual Friedman test was positive. In only 4, however, was decidua present in the uterus, the other 3 uteri containing a proliferating endometrium. In one case decidua was present on the surface of the ovary even though it was absent inside the uterus (see Fig. 1, A, B, C).



Fig. 1A.

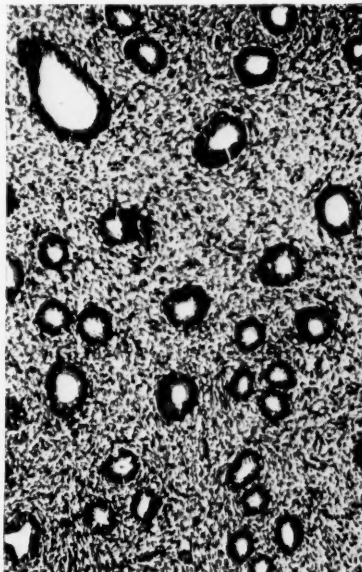


Fig. 1B.

Fig. 1A.—Perfect placental tissue and membranes in the Fallopian tube. The chorionic villi show no evidence of degeneration. While such well-preserved placental tissue is usually associated with uterine decidua, in this case the uterus contained a proliferating endometrium. Undegenerated placental tissue, as here pictured, was always associated with a positive Friedman test.

Fig. 1B.—Proliferating endometrium obtained by curettage in an ectopic pregnancy. Same patient as Fig. 1, A. Proliferating endometrium in the uterus is usually associated with moderately or markedly degenerated placental tissue in the tube, but in this case the placental tissue showed no evidence of degeneration.

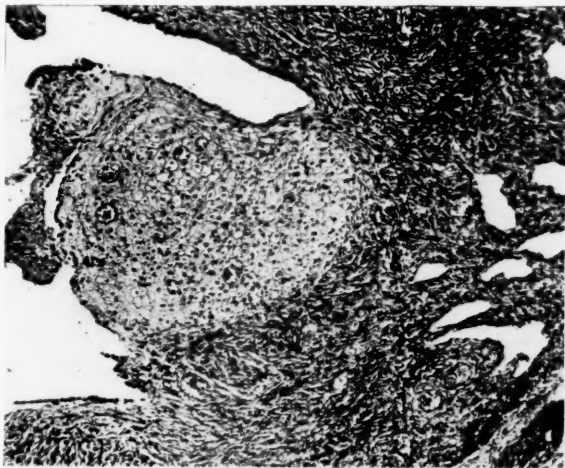


Fig. 1C.—Decidua on the surface of the ovary, a frequent finding in tubal pregnancy. Same patient as Figs. 1, A and B. In this patient decidua was absent in the uterus even though it was present on the ovary. This means that factors other than placental degeneration may also be important in causing degeneration or extrusion of uterine decidua.



In the cases designated as slight placental degeneration, many chorionic villi were perfectly preserved or slightly fibrotic, while others were markedly degenerated. Here it was felt that the Friedman test should be positive. There were 15 such patients, and the



Fig. 2A.

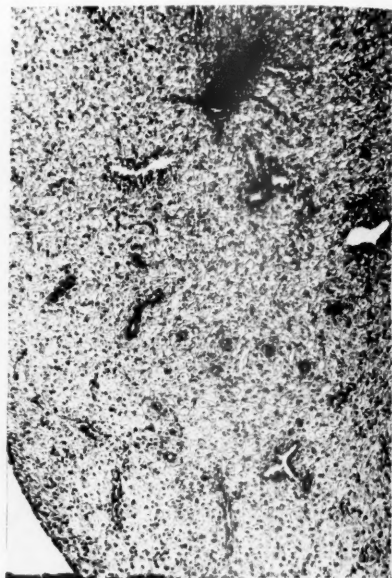


Fig. 2B.

Fig. 2A.—A combination of well-preserved and markedly degenerated placental tissue. For the purpose of our classification this was considered "slight" degeneration and was almost always associated with a positive Friedman test and usually with uterine decidua.

Fig. 2B.—Uterine decidua in ectopic pregnancy, obtained by curettage. Same patient as Fig. 2, A. Decidua was never present in the uterus if the placental tissue was more than "slightly" degenerated.



Fig. 3.—Markedly degenerated chorionic villi in the Fallopian tube with an occasional small island of well-preserved syncytial and Langhans cells. In our classification this degeneration was considered "moderate" in amount. In such cases it is believed that the Friedman test cannot be safely predicted. It was negative, however, in three out of four such cases. Decidua was always absent with this degree of placental degeneration.

Friedman test was actually positive in 14. In 10 the uterus contained decidua while in 5 it was absent (see Fig. 2, A, B).

Those placental tissues designated as marked degeneration consisted chiefly of shadow villi. With this degree of degeneration it was felt that the Friedman test should be negative. There were 5 such cases. In 4 the actual Friedman test was negative. In none of the 5 patients was decidua present in the uterus (see Fig. 4, A, B).



Fig. 4A.



Fig. 4B.

Fig. 4A.—Markedly degenerated shadow villi in the Fallopian tube with no evidence of active chorionic cells. Such placental tissue was considered "markedly" degenerated. In these cases it is felt that the Friedman test should be negative, and this was true in four out of five patients. When the tubal placental tissue was "markedly" degenerated, decidua was always absent in the uterus. In this patient the endometrium was in the early secretory stage.

Fig. 4B.—Early secretory endometrium. Same patient as Fig. 4A. Proliferating endometrium was more commonly found than secretory in the presence of degenerating ectopic pregnancies. The presence or absence of uterine decidua is related to the amount of blood lost per vaginam, the greater the blood loss, the less the chance for decidua to be present.

In the placental tissue designated as moderately degenerated, the chorionic villi were in a stage of degeneration between those designated as slightly and those designated as markedly degenerated. Here, for the most part, the chorionic villi were markedly degenerated, but there were occasional small groups of syncytial or Langhans cells that appeared viable. In this group of cases, the expected Friedman test was recorded as doubtful, for it was felt that a reasonably accurate prediction on the outcome of the biologic reaction could not be made. There were 4 such cases. In 3 the actual Friedman test was negative and in one positive. In all 4, decidua was absent in the uterus (see Fig. 3).

In all of the cases except two, the Friedman test was performed within a few days prior to operation; in these 2 cases (Cases 28 and 30 in Table II) misled by a negative Friedman test, laparotomy was delayed

several weeks. Had more microscopic sections through the placental tissue been taken, we believe that our results might have been even more accurate. At any rate, our results indicate a close but not perfect relationship between the state of preservation of the chorionic tissue and the outcome of the Friedman test.

As already noted, the state of preservation of the placental tissue is not always directly related to the presence of uterine decidua. Morphologically perfect placental tissue may be present in the Fallopian tube, and yet decidua may be absent in the uterus, even though decidua be present on the surface of the ovary. On the other hand, uterine decidua may persist in spite of the fact that many chorionic villi may be degenerated. Whenever, in our series, all of the tubal placental tissue was markedly degenerated, uterine decidua was always absent. Long ago Watson showed that the death of the embryo is followed by degeneration of the placenta. It is believed that a decrease in the production of the chorionic and corpus luteum hormones causes the degeneration of the decidua and its expulsion from the uterus, and no doubt this is true. There must, however, be other factors involved in order to explain the discrepancy that may exist between the state of preservation of the placental tissue in the tube and the presence or absence of decidua in the uterus. Among these factors may be included: the suddenness or rapidity with which the placental tissue degenerates or becomes isolated by clot and fibrin from the maternal circulation. It is also conceivable that a hyper-irritable uterus might expel a decidual cast without any appreciable degeneration of placental tissue while a uterus of lower sensitivity might require considerable degeneration of placental tissue before the decidua disappears.

In the three patients with perfect chorionic villi and no uterine decidua, one might wonder whether the decidua actually developed. Judging, however, by the relatively excessive amount of bleeding per vaginam, the decidua probably had been present and had been extruded from the uterus. Moritz and Douglas reported 6 cases without decidua in which there was no history of bleeding or desquamation from the vagina, but we have seen no such cases, and their occurrence, though possible, must be exceedingly rare.

Of the 32 cases studied, 3 patients were operated upon on the day of admission and 8 within one week; 17 were observed from one to two weeks, and 4 from two to nine weeks before operation was performed. Although there is no expectant treatment for ectopic pregnancy, if the diagnosis is established, it would nevertheless appear that the degenerative type of extrauterine gestation can be observed in the hospital with comparative safety for a reasonable period of time until the diagnosis is made. For there were no deaths in this series, and no serious sequelae followed even prolonged observations. All 32 patients were discharged within fifteen days after operation except for one who developed a rather superficial wound infection and remained in the hospital an additional week. We agree with Siddall and Jarvis that a proper curettage in ectopic pregnancy is not deleterious.

The admission temperature is of no value in predicting the presence or absence of decidua in ectopic pregnancy.

On admission 23 patients had a normal temperature and 10 of them had decidua at the time of curettage, an incidence of 43.5 per cent. Nine patients had an admission temperature of 100° to 102° F., and 4 of these had decidua, an incidence of 44.4 per cent. If, however, a patient is observed for a period of five or more days, it appears from a small series of cases that the presence of a persistently normal temperature is a slight point in favor for, and fever a point against, the finding of decidua. Of 14 patients with a normal temperature during such a period of observation, 6 (43 per cent) had decidua, whereas of 9 with a fever up to 101° only 2 (22 per cent) showed decidua.

Of the 32 patients studied only 8 had 400 c.c. or more blood in the peritoneal cavity at the time of operation. In six of these the correct diagnosis was made within a week and laparotomy promptly performed. These constitute the more acute ectopics of this series, and four of them were interstitial pregnancies. In two patients with 400 c.c. or more blood in the peritoneal cavity, the correct diagnosis was missed, due chiefly to reliance on a negative Friedman test, one patient being observed in the hospital for four weeks and one for nine weeks before operation was performed. In these two patients aspiration of the cul-de-sac might have established the diagnosis and shortened the period of observation. Where an ectopic gestation is strongly suspected, even in the presence of a negative Friedman test, aspiration of the cul-de-sac would appear to be indicated. In such cases with a negative Friedman, curettage would show no decidua, but nevertheless might be of value to rule out an old incomplete abortion or placental polyp.

Studies were also made of the leucocytic count of the blood and of the erythrocytic sedimentation rate. They were absolutely of no value in predicting the state of degeneration of the placental tissue, the outcome of the Friedman test, or the presence or absence of decidua.

It is often stated that a previous attack of salpingitis predisposes to the occurrence of an ectopic pregnancy. Microscopic examination of the tube containing the gestation is often of disputed value in proving the presence or absence of a previous infection in that tube, due to the distortion of the plicae and leucocytic infiltration that may accompany a tubal pregnancy. In our series, however, laparotomy revealed in 20 of the 32 patients incontestable gross evidence of a previous inflammation of the tube not containing the pregnancy, such evidence being clubbing of the tube, closure of the fimbriated extremity, or marked peritoneal adhesions about the tube. Four patients of the series had had a previous tubal pregnancy on the opposite side with the removal of the involved salpinx.

The simultaneous occurrence of a tubal and intrauterine gestation has often been reported. In one of our cases of ampullary tubal pregnancy with internal rupture, chorionic villi were found in the uterine cavity as well as in the salpinx. In this particular case, we do not believe that two pregnancies existed but that chorionic villi were extruded from the tubal lumen into the uterine cavity, for the placental tissue in the uterus appears entirely unrelated and unattached to the decidua. Regardless of the explanation, it should be remembered that very occasionally placental tissue can exist simultaneously in both the tubal and uterine lumina.

## SUMMARY

1. Thirty-two cases of ectopic pregnancy with complete clinical and laboratory findings are analyzed with regard to the findings on curettage, the result of the Friedman test, the microscopic examination of the removed tube, and the clinical picture.

2. Any patient with an ectopic pregnancy who bleeds scantily, even for many weeks, may still have uterine decidua, but with a decreased decidual expectancy as the duration of the bleeding increases. If the bleeding has been moderate or profuse for more than three weeks, decidua is extremely likely to be absent. The probable presence of uterine decidua is inversely proportional to the total amount of blood lost per vaginam, the less the blood loss, the greater the chance for decidua to be present.

3. No patient with a negative Friedman test had uterine decidua at the time of curettage. No patient with uterine decidua had a negative Friedman test.

4. There is a close but not perfect relationship between the result of the Friedman test and the state of preservation of the chorionic villi.

5. Occasionally one finds morphologically perfect placental tissue in the Fallopian tube, a positive Friedman test, and an absence of decidua in the uterus. Such patients always had a history of prolonged or profuse bleeding per vaginam.

6. Factors other than placental degeneration are probably important in causing decidual degeneration and expulsion. Among such factors may be the suddenness of placental degeneration, and the sensitivity and irritability of the decidua or myometrium.

7. In a well-regulated hospital, a suspected case of ectopic pregnancy without acute symptoms may be observed with comparative safety for rather prolonged periods of time until the diagnosis is made. Seventeen patients were observed from one to two weeks and 4 patients still longer, without serious sequelae.

8. If while under observation for several days or longer the patient's course has been febrile, the uterus appears less likely to contain decidua than if the temperature had remained normal.

9. In cases of suspected old ectopic pregnancy where the Friedman test is negative, aspiration of the cul-de-sac may confirm the diagnosis. Here curettage would reveal no decidua, but may nevertheless be indicated to rule out the presence of an old incomplete abortion or placental polyp.

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## EVALUATION OF STILBESTROL AS A THERAPEUTIC ESTROGEN

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IN 1938, Dodds and his co-workers<sup>1, 2</sup> reported the synthesis of 14:4' dihydroxy-a:B-diethyl stilbene, a compound unrelated chemically to natural estrogens which, however, possesses estrogenic properties. The following year, numerous clinical reports<sup>3-10, 16-19</sup> attested to the fact that, in the human being, stilbestrol was capable of relieving menopausal symptoms. However, a number of the patients developed toxic symptoms, the incidence of which seemed to vary considerably in the various series of cases reported. In a preliminary report,<sup>6</sup> presented before the New York State Medical Society, in April, 1939, we stated that the high incidence of toxic symptoms, which accompany the use of stilbestrol, constituted a serious objection to its use clinically. In this communication, we wish to report in detail the results of our further experience with stilbestrol, supplemented by morphologic studies of the endometrium, vaginal mucosa, and gonadotropic hormone assays.

### MATERIAL

This study was conducted on a group of 45 patients and includes the series reported in the preliminary communication. The patients varied in age from 24 to 72 years. The duration of the menopause varied from six months to nineteen years. There were 22 spontaneous postmenopausal patients, 9 surgical castrates, 6 x-ray castrates, and 8 patients who were still menstruating but who had menopausal symptoms. The symptoms varied considerably in nature and intensity. The most common symptom was flushes, which were present in 39 patients. The other symptoms noted were headache in 7; vaginal pruritus in 7; vertigo in 8; weakness in 6; arthralgias in 4; urinary symptoms in 2; insomnia in 3; and vaginitis and dyspareunia in 2.

### DOSAGE

Diethyl stilbestrol\* was administered orally and intramuscularly in varying doses. The oral dose varied from 0.3 mg. to 6 mg. daily, and the intramuscular dose varied from 1 to 5 mg., given from 1 to 3 times weekly. The total dosage varied from 7 mg. to 424 mg. The patient who received the largest total dose was treated over a period of five months. The longest duration of treatment was nine months in one patient who received a total of 177 mg.

In the evaluation of the efficacy of stilbestrol as a therapeutic agent, it was felt desirable to employ objective criteria of its action in addition to clinical evidence of improvement. The objective criteria employed were: vaginal smears, vaginal biopsies, endometrial biopsies and gonadotropic hormone studies.

\*For the stilbestrol used in this investigation, we are indebted to Mr. J. Hutchinson, Ayerst, McKenna and Harrison, Rouses Point, N. Y. and to Dr. J. A. Morrell, E. R. Squibb and Sons, New York City.

## VAGINAL SMEARS

The vaginal smears were prepared according to the method described in previous communications.<sup>11, 20</sup> In 15 patients there was evidence of a moderate estrogen deficiency in the vaginal smear, as manifested by the presence of a few small deep "atrophy" epithelial cells and leucocytes. In 11 patients the vaginal smears exhibited many "atrophy" epithelial cells and leucocytes, indicative of an advanced estrogen deficiency (Fig. 1). The vaginal smears of the remaining 19 patients fell into the borderline group and could not be classified definitely as showing estrogen deficiency or evidence of full estrogen effect.

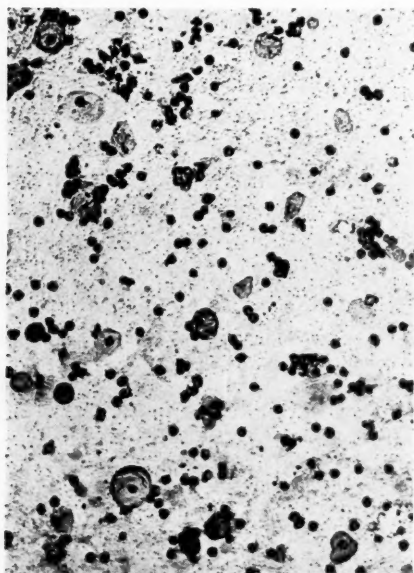


Fig. 1.

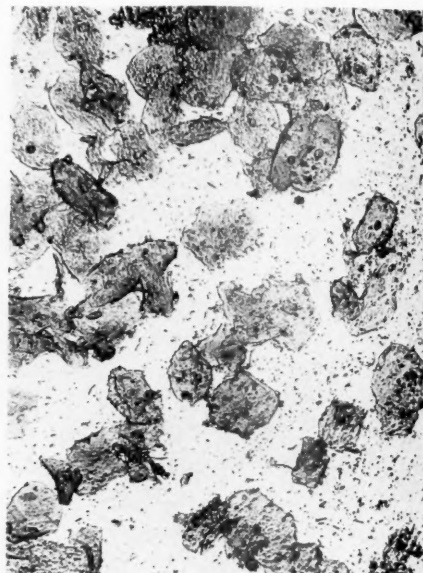


Fig. 2.

Fig. 1.—Case L. W. (Aged 53 years; four years postmenopause.) Preliminary smear indicative of advanced estrogen deficiency. Note "atrophy" cells and leucocytes.

Fig. 2.—Case L. W. Vaginal smear following the administration of 5 mg. of stilbestrol over a period of four days. Note the large, squamous cells with indistinct small nuclei and absence of leucocytes and "atrophy" cells.

Signs of an estrogenic effect, characterized by the increase in size and number of the large, squamous, epithelial cells and a diminution in the number of leucocytes and deep "atrophy" cells, were noted as early as four days following the administration of stilbestrol. Doses of 5 to 10 mg., given over a period of four to ten days, were sufficient to induce a full estrogenic smear characterized by the absence of leucocytes and deep "atrophy" cells (Fig. 2) and the predominance of large squamous cells with very small nuclei. Smears indicative of a full estrogenic effect persisted while stilbestrol was being administered. Following the discontinuation of treatment, the vaginal smears began to show signs of regression to their former deficiency state within fifteen to twenty days.

## VAGINAL MUCOSA

Vaginal biopsy studies were made on a group of 11 biopsies taken from 5 different patients. In each case, definite morphologic changes, indicative of a strong estrogen effect, were induced following the administration of stilbestrol. Fig. 3 shows a preliminary vaginal biopsy, obtained from Case S. R., characterized by a narrow epithelial layer, consisting chiefly of a basilar zone (5 to 6 cell

layers thick) and the absence of a cornified and vacuolated zone. In addition, there is considerable round cell and leucocytic infiltration of the intraepithelial and subepithelial zones, characteristic of chronic and subacute senile vaginitis.

Following the intramuscular injection of 20 mg. of stilbestrol in two days, a biopsy on the fifth day revealed a tremendous increase in thickness of the epithelium, due chiefly to the appearance of a wide vacuolated zone and increased cellularity of the basalis. In addition, there was a downgrowth of the papillae and a disappearance of leucocytes (Fig. 4).

In another patient (O. W.), a vaginal biopsy taken following the administration of 113 mg. of stilbestrol over a period of seven months revealed a mucosa of normal thickness, a well-defined cornified zone and intraepithelial zone and a normal basalis. There was no evidence of abnormal cellular proliferation.



Fig. 3.

Fig. 3.—Case S. R. (Aged 60 years; twelve years postmenopause.) Preliminary vaginal biopsy, showing moderate degree of atrophy. Note the narrow epithelial layer; absence of cornified and vacuolated zones; presence of subepithelial and intraepithelial round cell infiltration.

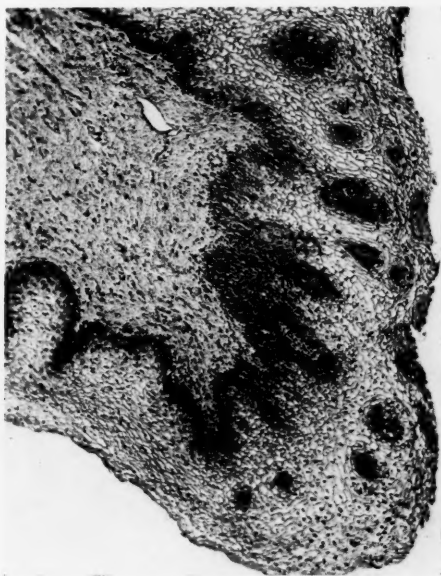


Fig. 4.

Fig. 4.—Case S. R. Vaginal biopsy following 20 mg. of stilbestrol administered intramuscularly over a period of two days. Note the wide vacuolated zone and increased cellularity and proliferative activity of the basalis.

#### ENDOMETRIUM

Uterine bleeding is not uncommon following the administration of naturally occurring estrogens. In this series of cases, uterine bleeding occurred 5 times in 4 different patients. The smallest amount of stilbestrol which induced uterine bleeding was 20 mg., given intramuscularly. This occurred in a 52-year-old patient (natural menopause, six years), who was given 10 mg. of stilbestrol in 2 successive days. On the third morning, uterine bleeding began and lasted six days.

In another patient, bleeding of four days' duration occurred following the administration of 228 mg. of stilbestrol, given orally, over a period of two and one-half months. Bleeding then stopped for seven days. Following the re-administration of 12 mg. of stilbestrol, orally, over a period of three days, bleeding

recurred. In no instance was the bleeding sufficiently severe to be of serious consequence. Nevertheless, the stilbestrol was usually discontinued with the onset of bleeding.

In most cases, the bleeding occurred during the period of stilbestrol administration. There is apparently a wide variation in the dosage necessary to induce uterine bleeding. In this series, as noted above, the dose varied from 20 mg. to 228 mg. and, in other patients, doses of comparable and larger magnitude did not induce uterine bleeding.



Fig. 5.—Case S. R. Preliminary atrophic endometrium.

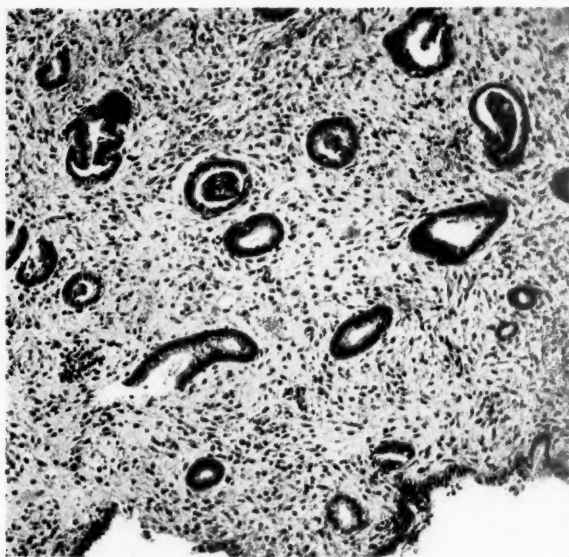


Fig. 6.—Case S. R. Endometrial biopsy following 20 mg. of stilbestrol, intramuscularly, showing slight proliferative changes.

Eleven endometrial biopsies were taken on 6 different patients. In each of them, various degrees of proliferation were induced, varying from slight to advanced proliferation resembling hyperplasia. These effects were produced with stilbestrol administered both orally and intramuscularly. Four of the endometrial biopsies were taken during periods of bleeding. There is, apparently, no relationship be-

tween the morphologic state of the endometrium and the bleeding, since the histologic picture varied from slight proliferation to moderate and advanced proliferation. On the other hand, one patient, following 75 mg. of stilbestrol, showed a hyperplastic endometrium (Fig. 8) without uterine bleeding. There appears to be considerable individual variation in the response of the endometrium to stilbestrol. In one instance, 128 mg. produced slight proliferation, whereas, in another case, 29 mg. were sufficient to produce advanced proliferation.

In one patient, an unusual endometrial pattern was found which will be described here. A preliminary endometrial biopsy on November 25 revealed atrophy (Fig. 5). On November 28 and 29, the patient received 10 mg. of stilbestrol, intramuscularly. Spontaneous uterine bleeding occurred on December 1 and continued for six days. An endometrial biopsy, done on the first day of bleeding, revealed a moderate amount of proliferation (Fig. 6). The stilbestrol was continued in 5 mg. doses daily from December 1 to 6. Another biopsy on December 6 revealed



Fig. 7.

Fig. 7.—Case S. R. Endometrial biopsy following 55 mg. of stilbestrol, showing a mixed picture of proliferative and secretory changes.

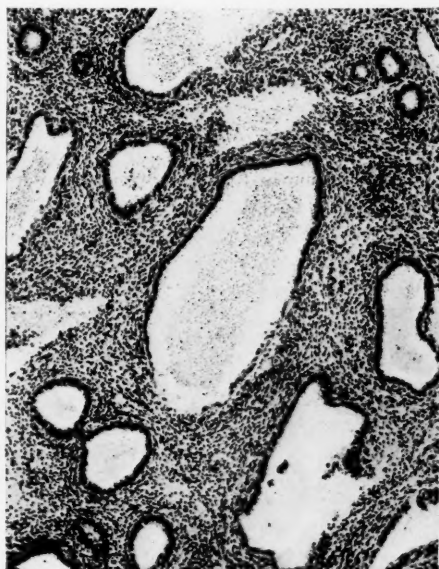


Fig. 8.

Fig. 8.—Case C. C. (Aged 48 years; two years postmenopause.) Endometrial biopsy following 75 mg. of stilbestrol, showing advanced proliferation with cystic glands resembling hyperplasia.

an atypical endometrial pattern (Fig. 7). There was a marked increase in the size and number of endometrial glands. Many of the glands were dilated, showed marked vacuolization and pseudostratification. The stroma was edematous and showed increased cellularity. A glycogen stain demonstrated the presence of varying amounts of glycogen. The histologic appearance of this endometrium did not resemble any normal phase or any pattern induced by natural estrogens. The histologic appearance consisted of a combination of marked secretory activity with moderate proliferation. On December 18 and 20, the patient was again given 10 mg. of stilbestrol. On December 26 uterine bleeding recurred and continued for ten days. On January 3 an endometrial biopsy revealed moderate proliferation with no evidence of secretory changes.



## GONADOTROPIC HORMONE STUDIES

It has previously been demonstrated that the excessive production of castrate gonadotropic factor in the menopause can be inhibited by the administration of adequate amounts of estrogens.<sup>12-14</sup> Gonadotropic hormone studies were performed on 8 menopause patients in this series to determine whether stilbestrol could inhibit the excessive production of gonadotropic hormone by the pituitary. A modification of the alcohol-acetone precipitation method was employed for the extraction of the castrate gonadotropic factors from the urine.<sup>15</sup> Hormone studies were discontinued in 3 of the patients because they developed severe toxic symptoms. In only one of the remaining 5 patients did the castrate gonadotropic hormone disappear from the urine. This patient was given a total of 50 mg. of stilbestrol in oil, over a period of forty-one days. The urine was negative for castrate gonadotropic hormone during the period of stilbestrol administration and for twenty-one days after the discontinuation of the treatment. The remaining 4 patients were given doses varying from 10 to 26 mg., over periods varying from twelve to forty-seven days, without appreciably affecting the castrate gonadotropic hormone excretion. A detailed report of the effect of stilbestrol upon gonadotropic hormone excretion in the menopause is being made elsewhere.

## THERAPEUTIC RESULTS

In this series of 45 patients, improvement was noted in 29; complete relief of symptoms in 8; and no improvement in 8. Improvement, if it did occur, took place within four to five days and maximum relief was achieved at the end of ten days to two weeks. The symptom most easily relieved was the flushes. If other symptoms were present, such as nervousness, weakness, vertigo, etc., they were apparently affected little, if at all. Following the discontinuation of treatment, the symptoms usually recurred within one to two weeks. The rapidity with which symptoms recurred after the discontinuation of the treatment was very striking in all but a few cases.

The sense of well being and increased strength and vigor that are frequently noted following the administration of naturally occurring estrogens were observed infrequently following the use of stilbestrol in this series of cases. In addition to the incomplete therapeutic effects of stilbestrol, toxic symptoms were encountered frequently. In view of the fact that these toxic symptoms seriously detract from the therapeutic value of stilbestrol, they will be presented in some detail.

## TOXIC SYMPTOMS

Toxic symptoms were noted in 29 patients (64 per cent). Nausea, vomiting, and vertigo, either singly or in combination, occurred most frequently (25 cases). Three patients complained of pain in the epigastrium and one patient had severe pain in the right upper quadrant, associated with nausea. Two patients had diarrhea in addition to nausea and vomiting. One patient complained of precordial pain, palpitation, and nausea following the ingestion of one tablet of 0.2 mg. of stilbestrol. In some cases toxic symptoms occurred within twenty minutes after oral administration. One patient developed painful edema of the vulva which persisted for two weeks after the discontinuation of therapy. In some patients, toxic symptoms occurred at the beginning of treatment but disappeared as the drug was continued. In contrast to these, some patients did not develop nausea until after the drug had been administered continuously for several days. One patient, who had received intramuscular injections for nine months with complete control of the flushes and without toxic symptoms, developed epigastric pain, nausea, and dizziness at the end of this time. The symptoms subsided within ten days after the stilbestrol was discontinued. The nausea and vomiting usually disappeared within twenty-four hours after discontinuation of the stilbestrol.

Although several theories have been advanced to explain the toxic symptoms (direct irritation of the gastric mucosa, liver damage, direct action on the central nervous system), there is little factual evidence to support them. In an attempt to determine whether the toxic symptoms were attributable to kidney or liver damage, MacBryde, Freedman and Loeffel,<sup>16</sup> Shorr, Robinson and Papanicolaou,<sup>17</sup> and Buxton and Engle,<sup>18</sup> performed liver function tests as well as blood chemistry and urine studies on patients receiving large doses of stilbestrol. None of these workers was able to obtain any evidence indicating liver damage. One of the patients, reported by Buxton and Engle, developed albuminuria during the course of treatment which disappeared after the discontinuation of the stilbestrol. Apparently there were no findings in any of the other cases to indicate impairment of kidney function.

#### DISCUSSION

It is difficult to explain the marked variation in the incidence of manifestations of toxicity, as reported by different investigators. It is not unlikely that the lack of agreement as to the incidence of toxic effects is not due entirely to variations in dosage or mode of administration but, rather, to personal differences in the evaluation of the symptoms.

It appears that although stilbestrol has estrogen-like properties, as manifested by its proliferative action on the endometrium and vaginal mucosa, it is not a satisfactory therapeutic substitute for the estrogens of the estradiol family. This conclusion is based on the fact that the therapeutic effects of stilbestrol were, in most instances, neither complete nor uniform. Furthermore, it induced toxic symptoms in a large percentage of cases. In this connection, it should be borne in mind that treatment with estrogens is essentially substitution therapy and, for this reason, not infrequently entails the use of the hormone over long periods of time. Moreover, in view of the paucity of information concerning the origin and mechanism of the toxic symptoms induced by stilbestrol, we feel that its use, for the present, should be confined to experimental studies. The synthesis of stilbestrol by Dodds and his co-workers constitutes a brilliant achievement of modern chemistry. It is hoped that further investigations will yield a compound which will preserve the biologic properties of stilbestrol without its distressing clinical by-effects.

#### SUMMARY AND CONCLUSIONS

1. The biologic and therapeutic properties of stilbestrol were studied in a series of 45 cases. These studies included (a) an evaluation of its effect on the vaginal smear, vaginal mucosa, and endometrium; (b) the capacity of stilbestrol to inhibit the excessive gonadotropic hormone excretion in the menopausal patient; and (c) its effectiveness in relieving the symptoms of the menopause syndrome.
2. These studies have shown that (a) stilbestrol has an estrogen-like effect on the human vaginal mucous membrane and endometrium; (b) if sufficient stilbestrol is administered, it appears to inhibit the excessive gonadotropic hormone in the menopause patient; (c) stilbestrol relieves the hot flushes of the menopause, but it does not im-

part to the patient the feeling of well-being and nervous stability that usually result from treatment with the natural estrogens.

3. Toxic symptoms were observed in 64 per cent of the 45 patients.

4. The toxic symptoms most commonly noted were nausea, vomiting, and vertigo.

5. The high incidence of toxic symptoms, in our opinion, militates seriously against the usefulness of stilbestrol as a therapeutic agent.

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### A CRITICAL ANALYSIS OF CESAREAN SECTION IN A LARGE MUNICIPAL HOSPITAL\*

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**A** PERUSAL of the current literature conveys the impression that the maternal risk of cesarean section is less than 3 per cent.<sup>1, 3, 8, 11, 12, 15</sup> Occasionally a maternal mortality rate of 5 per cent and 6 per cent is acknowledged.<sup>2</sup>

The maternal mortality studies of large communities,<sup>5, 16, 17</sup> which more truly reflect the results for obstetrics as it is generally practiced, yield much higher rates and substantiate the contention of Watson<sup>1</sup> that when all cases are included, the cesarean mortality for the United States is probably from 10 to 15 per cent.

If any advance is to be made in the reduction of cesarean mortality, it is important that every institution should, from time to time, review its records and present the facts for discussion, whether they be good or bad. Before judgment is passed, however, the critic should bear in mind that lower cesarean mortality rates are to be expected where elective sections predominate, and that the mortality percentage

\*Read at a meeting of the Section of Obstetrics and Gynecology, The New York Academy of Medicine, February 27, 1940.

is likely to rise when emergency and other nonelective sections constitute the greater proportion of cases.

This report is based on a review of all cesarean operations at Morrisania City Hospital, one of several municipal hospitals in the City of New York. The Obstetrical Service was organized in October, 1929. Up to Dec. 31, 1937 there were 14,489 deliveries. More than one-half of the obstetric admissions are referred from the Out-patient Antepartum Clinic. The remainder either apply directly or are transferred from other municipal hospitals. About 20 to 30 per cent of the in-patients are colored. The service is supervised by the attending staff, resident, and assistant resident.

#### STATISTICAL RÉSUMÉ

One hundred and twelve cesarean sections were performed, an incidence of 0.8 per cent, or 1 section in 129 deliveries. The average cesarean incidence in New York City is two to four times higher, or about 1 section in 25 to 50 deliveries. It would appear from this that we have either been very conservative in the management of the various obstetric difficulties for which cesarean section might be indicated, or that we have been rather fortunate in having a minimum of patients requiring this procedure. We believe that the explanation of our low incidence is due to a conservative policy. In fact from a consideration of the data which follow, we may have carried this policy too far in some instances.

Our uncorrected maternal mortality rate for cesarean section is 10.7 per cent. However, this high death rate is not reflected in our uncorrected general maternal mortality rate for the same period, which is 5.3 per thousand living births. This result compares favorably with that of other similar institutions.

The indications for which cesarean sections were done at our institution are enumerated in Table I.

TABLE I. INDICATIONS FOR CESAREAN SECTION

		NUMBER CASES	MATERNAL DEATHS
Cephalopelvic disproportion		47	6
Contracted inlet	42		
Contracted outlet	2		
Normal pelvis	3		
Previous cesarean section		19	1
Placenta previa		19	2
Central	15		
Partial	4		
Premature separation of placenta		10	2
Complete	9		
Partial	1		
Obstructing tumor		6	-
Cardiac disease		4	-
Eclampsia		1	1
Rupture of uterus		2*	-
Previous attempt at delivery		1	-
Vaginal stenosis		1	-
Cervical stenosis		3	-
Total		112	12

\*One case included in group of "previous cesarean section."

*Cephalopelvic Disproportion.*—This constituted the largest of the groups (41 per cent). The problem for the obstetrician is identical whether the baby is too large for the pelvis or the pelvis too small for the baby. Of the 47 pa-

tients operated upon for this indication, 6 women died, a maternal mortality rate of 12.7 per cent for the group.

In 11 instances the disproportion was absolute, and elective sections were done immediately on admission with no maternal or fetal deaths.

In the 36 patients with relative disproportion a test of labor was permitted before cesarean section was performed.

Some hospitals have a hard and fast rule that, unless rapid progress is made in six to eight hours, with intact membranes, a cesarean section is to be performed. With this yardstick the patient is operated upon under ideal conditions with a prognosis for recovery not less than 97 per cent. By the same token it is also quite obvious that many women so readily sectioned might conceivably have delivered spontaneously or with the assistance of forceps if given a longer test.

Our practice has been to individualize each case. The test lasted six hours, or even twenty-four hours, depending on the amount of progress made. Vaginal examinations were prohibited. Rectal examinations were done as often as required.

During the past few years our judgment has been somewhat influenced by x-ray pelvimetry. The method used is that described by Weitzner,<sup>7</sup> which gives a rapid and accurate measurement of the conjugata vera as well as a comprehensive view of the presenting part in its relation to the pelvic inlet.

By following this plan, most of our patients with relative cephalopelvic disproportion were successfully delivered by the vaginal route. In 1938, for example, of 47 full-term primiparas who began labor with an unengaged presenting part, only 2 required a cesarean section. The rest were delivered spontaneously or with forceps, with a loss of only 2 babies and no maternal mortality.

If insufficient progress was made during a test of labor, the baby was delivered by cesarean section (if alive), or by craniotomy (if dead). It is significant and interesting to note that during the period covered by this report craniotomy was resorted to only once.

Of the 36 patients with relative disproportion delivered by cesarean section, 6 died. Four of these deaths were due to peritonitis. The type of cesarean operation chosen was an important factor in causing the high mortality.

Approximately one-half of the 47 patients with cephalopelvic disproportion were operated upon by the classical and the other half by the low segment method (Table II). These operations were performed by the same members of the ob-

TABLE II. CEPHALOPELVIC DISPROPORTION, TYPE OF OPERATION

	CLASSICAL				LOW SEGMENT				PERITONEAL EXCLUSION			
Number of cases	22				24				1			
Primiparas	21				19				1			
Hours in labor	0	0-12	12-24	24+	0	0-12	12-24	24+	0	0-12	12-24	24+
Number of cases	2	9	7	4	-	3	8	13	-	-	-	1
Maternal deaths	-	2*	-	1*	-	1*	1*	1*	-	-	-	-
Hours membranes ruptured	0	0-12	12-24	24+	0	0-12	12-24	24+	0	0-12	12-24	24+
Number of cases	17	5	-	-	6	7	4	7	-	-	-	1
Maternal deaths	3*	-	-	-	-	1*	-	2*	-	-	-	-
Peritonitis	3*				1*				-			
Paralytic ileus	-				1*				-			
Pneumonia	-				1*				-			

\*Died.

stetric staff in the same hospital for the same indication, and are therefore comparable for evaluating the superiority of one operation over the other.

Those treated by the classical cesarean section had the advantage of intact membranes and shorter duration of labor. In spite of this, 3 patients (13.6 per



cent) died of peritonitis. Of the low segment group, only 1 patient (4 per cent) died of the same cause. The security against peritoneal infection for the low segment operation was three times greater than that for the classical cesarean section.

*Previous Cesarean Section.*—Of the total number of patients admitted to the hospital with a history of a previous section, 19 women required a repeated operation. Eighteen were registered in our Prenatal Clinic and were instructed to enter the hospital at the first sign of labor. Thus it happens that most of the patients were admitted under ideal conditions, with membranes intact and in labor less than six hours (Table III). One patient died, a mortality of 5.2 per cent for this group.

TABLE III. PREVIOUS CESAREAN SECTION, TYPE OF OPERATION

	CLASSICAL			TWO FLAP			PORRO		
	0	0-12	12-24	0	0-12	12-24	0	0-12	12-24
Hours in labor	10	6	-	-	1	1	-	1*	-
Maternal deaths	1	-	-	-	-	-	-	-	-
Hours membranes ruptured	Int.	0-6	6-12	Int.	0-6	6-12	Int.	0-6	6-12
Maternal deaths	14	1	1	2	-	-	1	-	-
Stillbirths	1	-	-	-	-	-	-	-	-
Neonatal deaths	0			0			1		
Peritonitis	0			0			0		
	1 (died)			0			0		

\*Ruptured uterus.

Our attitude toward patients who have been previously sectioned is more elastic than is permitted by the adage "once a cesarean, always a cesarean." If the previous section was performed for indications other than obstructed labor, and if the post-partum course was not complicated by morbidity, the patient was allowed a test of labor, *provided she remained under observation from the very onset*. If rapid and progressive advancement appeared within a relatively short time, delivery was allowed to be completed normally or assisted with forceps. If labor slowed up for any cause, a cesarean section was done.

For example, during the year 1934 alone, 7 patients were admitted with a history of having had a previous section. Three patients delivered spontaneously and one was assisted by forceps. The remaining three patients were subjected to section immediately on admission because of a contracted pelvis.<sup>6</sup>

One patient, a negress, disobeyed instructions and remained at home while in labor with the hope of delivering spontaneously. A few hours later the uterine scar gave way and she was brought to the hospital in shock due to a ruptured uterus and an intra-abdominal hemorrhage. A Porro section was done. The fetus was stillborn. The patient had a stormy convalescence but fortunately recovered.

The patient who died had a large incisional hernia which was repaired immediately after the section was completed. Autopsy examination indicated an extension of a *Staphylococcus aureus* infection of the abdominal wound into the general peritoneal cavity. The uterine incision was uninvolved. This death was preventable. It taught us to restrict our surgery during cesarean section to actual necessities, and postpone to some later date other procedures which increase the risk to the patient.

*Placenta Previa.*—(Table IV.) Nineteen patients with placenta previa were treated by cesarean section. Of these, 15 were central and 4 were partial. Two mothers died, one of embolism and one of peritonitis. The maternal mortality for this group was 10.5 per cent. The patient who died of peritonitis had a classical section within three hours of the initial hemorrhage and immediately after only one vaginal examination.

Six infants died. All were premature. Only 3 could be considered viable.

TABLE IV. PLACENTA PREVIA, TYPE OF OPERATION

	CLASSICAL			LOW SEGMENT			PERITONEAL EXCLUSION		
Number of cases	12			6			1		
Multiparas	6			6			1		
Months' gestation	7	8	9	7	8	9	7	8	9
Number of cases	1	6	5	-	2	4	-	1	-
Stillbirth	-	1	-	-	-	-	-	-	-
Neonatal death	1	3	-	-	1	-	-	-	-
Maternal death	-	-	2	-	-	-	-	-	-
Blood transfusion	3			4			-		
Peritonitis	1*			-			-		
Embolism	1*			-			-		

\*Died.

Cesarean section has been used mainly in the interest of the mother. We have adhered strictly to the principle of delivering all patients with central placenta previa by cesarean section no matter what the period of gestation.

The method of delivery in patients with partial placenta previa has been left to the discretion of the staff. Thus only 4 such patients were treated by cesarean section.

The recent literature indicates that many obstetricians are extending the use of cesarean section to include most cases of partial placenta previa and some of the marginal placenta previas.<sup>12-15</sup> It is conceivable that on further study of our statistics on placenta previa partialis, our indications for section may be broadened to include an increasing number of these cases.

The low segment operation was done in 6 instances and found to be as applicable for the treatment of this complication as the classical cesarean section except that more bleeding was encountered when the placenta was located under the line of incision.

*Premature Separation of the Placenta.*—Until recently all cases of the complete variety (ablatio placenta) have been treated by cesarean section. The milder or partial placental separations were all delivered vaginally.

Of the 10 patients sectioned, 2 died; 1 of peritonitis and the other of toxemia (Table V). Both were in poor condition at the time of operation notwithstanding previous transfusions. The maternal mortality for this group was 20 per cent.

TABLE V. PREMATURE SEPARATION PLACENTA, TYPE OF OPERATION

	CLASSICAL	LOW SEGMENT
Number of cases	8	2
Maternal deaths	2	-
Stillbirth	6	1
Neonatal death	1	1
Peritonitis	1*	-
Toxemia	1*	-

\*Died.

The superior results claimed by the advocates of the Dublin routine for the treatment of complete separation of the placenta have impressed us considerably. The technique consists of rupturing the membranes, packing cervix and vagina, repeated injections of pituitrin, application of a Spanish windlass, replacement of blood loss by large transfusions, and prompt delivery when full dilatation is obtained. We applied this routine in the last 3 cases of ablatio placenta seen on the wards. Our courage faltered after observing the first case for twelve hours as the patient seemed to be going downhill. She was delivered by a classical cesarean section. When the next 2 patients were admitted we determined to carry out the method to completion, and did. Both patients made an uneventful recovery.

It was a trying experience, for it meant constant surveillance and concerted cooperation on the part of the nursing and interne staffs. We feel that the Dublin method should be used only where blood transfusions can be readily obtained and where a trained personnel is always available. Lacking such facilities, the interest of the patient is best served by a cesarean section.

*Obstructing Tumors* (Table VI).—This group is mainly of interest because of the variety of pelvic masses found obstructing vaginal delivery. There were 2 cases of cervical fibromyomas, and one each of embryonal tumor of the ovary, dermoid cyst of the ovary, pelvic kidney, and retroperitoneal sarcoma.

TABLE VI. OBSTRUCTING PELVIC TUMORS

Cervical fibromyoma	2 cases
Embryonal tumor of ovary	1 case
Dermoid cyst of ovary	1 case
Pelvic kidney	1 case
Retroperitoneal sarcoma	1 case

There were no maternal deaths. The one neonatal death resulted from prematurity.

*Cardiac Disease.*—Cesarean section as means of terminating labor in patients with heart disease was resorted to in four instances. One case was a primiparous cardiac who had been hospitalized for twenty-four days because of decompensation. The other three were multiparas with histories of previous decompensations in whom sterilization was advocated and a cesarean section done, therefore, at term to effect this procedure.

All these patients were functionally classified as Class 2b. In spite of a poor myocardium they were able to withstand the strain of the operation. One patient eviscerated on the twenty-first day postoperative, then developed a bronchopneumonia and pleural effusion, but survived. The case illustrates the difficulty of judging the cardiac reserve until the heart is actually under stress.

The classical section was employed in each instance because of the rapidity with which it can be performed and because of the access to the Fallopian tubes. There were no maternal or fetal deaths in this small group.

A point worth emphasizing is the choice of anesthesia and the manner of its administration. Patients with heart disease are very prone to develop pulmonary complications. For this reason the anesthesia should be given by an expert anesthetist. We prefer the use of gas-oxygen inhalation.

*Eclampsia.*—We have not found it necessary to resort to cesarean section for pre-eclampsia. Our experience with a modified Stroganoff regime followed by induction of labor has proved most satisfactory.

Perhaps the same conservative attitude may also be taken with the convulsive states. We had an unfortunate experience with the only patient with eclampsia who was treated surgically. This woman, a nonclinic primipara, was admitted to the hospital in coma, with frequent convulsions and was practically moribund. Examination revealed her to be at term and not in labor. A classical cesarean section was done under ethylene anesthesia but the patient died twenty-four hours later.

*Rupture of the Uterus.*—Included in this series are two cases of rupture of the uterus. One occurred through a previous cesarean scar. The other had a spontaneous rupture of the uterus. This patient, a thirty-six-year-old multipara, was admitted to the hospital in shock after having had abdominal pains for eight hours. The cervix was 1 finger dilated, membranes were intact, presenting part unengaged, and there was no external evidence of bleeding. She was given a transfusion but failed to rally. The diagnosis of rupture of the uterus was then suspected and a laparotomy performed. Free blood was present in the peritoneal cavity and found to originate from a tear in the anterior wall of the uterus. A stillborn baby was delivered through this tear and the uterus closed in layers. Convalescence was uneventful.

*Unsuccessful Attempt at Delivery.*—The danger of performing a cesarean section, after previous attempts at delivery have been unsuccessful, is appreciable. Kerr<sup>4</sup> quotes maternal mortality rates under such conditions as high as 15 to 20 per cent. He advocates craniotomy as the method of choice, because the fetus is dead as a rule, and the risk is less unless the pelvis is markedly contracted.

Our experience at Morrisania City Hospital with this type of patient has been limited to 2 patients, both of whom were admitted in shock. One was treated by craniotomy. The other was subjected to a Hirst peritoneal exclusion operation because of extensive bladder injury which followed an attempted version in another hospital. The trauma to the bladder precluded any possibility of doing a Latzko or a low segment operation. Both these patients recovered after a stormy convalescence.

*Stenosis of the Vagina and of the Cervix.*—A douche of undiluted lysol in an attempt to produce an abortion resulted in an extensive cicatrization of the vagina in one case which made cesarean section mandatory.

Three patients with cervical stenosis due to a previous trachelectomy were delivered by vaginal section in one instance and by abdominal section in two.

There were no maternal or fetal deaths in this group.

*Maternal Mortality.*—The cause of our maternal deaths following cesarean section are listed in Table VII. Peritonitis took the heaviest toll, accounting for

TABLE VII. CAUSES OF DEATH

	TOTAL CASES	INDICATION FOR OPERATION					TYPE OPERATION	
		PREV. SECT.	CONT. PELVIS	PLAC. PREV.	PRE. SEP. PLACENTA	ECLAMPSIA	CLASSICAL 70 CASES	LOW SEGMENT 37 CASES
Peritonitis	7	1	4	1	1	-	6 (8.5%)	1 (2.7%)
Pulmonary embolus	1	-	-	1	-	-	1	-
Paralytic ileus	1	-	1	-	-	-	-	1
Bronchopneumonia	1	-	1	-	-	-	-	1
Toxemia	2	-	-	-	1	1	2	-

7 (58.3 per cent) of the 12 deaths. At least two of these deaths may be considered as preventable, because autopsy revealed the infection to have been introduced at the time of operation.

The two patients who died of toxemia were critically ill at the time of admission and died in less than twenty-four hours. The eclamptic patient was not a suitable risk for abdominal surgery. The operation was used as a measure of last resort since death appeared inevitable.

#### DISCUSSION

The prevention of peritonitis deserves intensive investigation as it causes from 40 to 50 per cent of deaths following cesarean section.<sup>5, 8, 15</sup>

The relation of ruptured membranes, duration of labor, and vaginal examination to the spread of infection during labor requires no discussion. Their importance has been adequately stressed by previous studies and needs no further emphasis here.

Two other factors, however, have played a prominent role in our incidence of peritonitis, namely: introduction of infection at the operating table; and type of operation selected.

The incidence of our wound infections, which fortunately consisted mostly of mild stitch abscesses, was close to 20 per cent in spite of the

most rigorous precautions in preparing the abdomen for operation. Autopsies on two of the seven deaths from peritonitis clearly indicated an extension of the infection from the abdominal wound to the general peritoneal cavity.

In checking over the possible sources for this break in technique, the operating room itself came under suspicion. The hospital has two major operating rooms for the use of all surgical cases. As less than 50 per cent of our cesarean sections were elective, not infrequently the operation followed shortly after a potentially or actually infected surgical case. The nursing personnel remained the same for both operations. It is not difficult, therefore, to imagine cross-infection under such circumstances.

We believe, with DeLee and others, that the obvious remedy is a complete operating room unit for the exclusive use of cesarean section, with nursing personnel devoted only to this division. Arrangements to incorporate such a unit on our obstetric floor have already been made.

The second factor of importance affecting the incidence of peritonitis is related to the type of cesarean operation selected. The classical cesarean section was performed on 70 patients. Six died of peritonitis, a maternal death rate of 8.5 per cent. The low segment operation was performed 37 times with one death from peritonitis, a maternal death rate of 2.7 per cent.

As was described under "cephalopelvic disproportion," the conditions under which the low segment operation was performed were less favorable than those of the classical group. Nevertheless, notwithstanding this disadvantage, the low segment operation gave three times more security against the occurrence of peritonitis.

The classical cesarean section should be utilized only where speed is necessary or where it is essential to perform other operative procedures. It is safer for the patient, however, to resort to the low segment operation, the Latzko extraperitoneal operation, or the approach to the lower uterine segment recently described by Waters.<sup>9</sup>

The final criterion of obstetric management does not rest on the end results of any one operative procedure but on the outcome of all deliveries, normal or otherwise. This information may be obtained from general maternal mortality rates which are uncorrected. In New York City, this rate is said to be 6.1 per thousand living births.<sup>5</sup> In the very best hands in English hospitals, the rate is 5.8.<sup>10</sup> At Morrisania City Hospital, the rate is 5.3, notwithstanding a relatively high maternal mortality for cesarean operations. Therefore, we feel justified in maintaining our present policy toward the obstetric patient, except for the few changes already mentioned.

#### SUMMARY AND CONCLUSIONS

1. An analysis of cesarean sections at Morrisania City Hospital is presented. The incidence of this operation is 0.8 per cent, or one in 129 deliveries. The uncorrected cesarean maternal mortality rate is



10.7 per cent. The general uncorrected maternal mortality rate for all deliveries, spontaneous and operative, is 5.3 per thousand living births.

2. The indications for cesarean section are separately considered and the errors in judgment and technique discussed.

3. The superiority of the low segment operation over the classical section is confirmed.

4. The role of peritonitis as a cause of maternal mortality following this operation is stressed. The probable causes for this complication at Morrisania City Hospital are enumerated and the methods described whereby its occurrence may be reduced.

The authors wish to acknowledge the assistance of Dr. Milton J. Goodfriend in organizing the material for this paper.

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### MIXED ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA OF THE UTERUS\*

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**M**ALIGNANT neoplasms are occasionally found in which there is differentiation into a type of cell entirely foreign to the organ in which it is primary. Some of these neoplasms can be explained as arising in teratomas while in others no such explanation is possible. Primary osteogenic sarcomas have been described in the thyroid gland (Broders and Pemberton<sup>1</sup>) and in the breast. Squamous cell carcinomas are of frequent occurrence in the bronchus and yet squamous epithelium is not normally found here. Squamous epithelium has been described in the gall bladder (Broders<sup>2</sup>), prostate (Burrows and Kennaway<sup>3</sup>), ducts of the pancreas, and gastrointestinal tract (Vinson and Broders<sup>4</sup>).

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Squamous cell carcinomas have been demonstrated to occur in all of these locations. Occasionally a carcinoma develops in an organ containing glandular epithelium in which a portion of the tumor retains the glandular character of the epithelium from which it arises while the cells in another part differentiate into pearly bodies and assume the characteristics of malignant squamous epithelial cells. For this type of neoplasm the terms "adenocarcinoid" and "adenocanthoma" have been coined.

#### REVIEW OF LITERATURE

The replacement of columnar epithelium by benign squamous epithelium in the uterus has been given various names, including *ichthyosis uteri*, *psoriasis uteri*, *epidermization*, *squamous metaplasia*, *leucoplakia*, *epidermalization*, and *epidermoidization*. Gautier,<sup>5</sup> at the International Medical Convention at Geneva, was the first to describe a case in which the uterine cavity was lined by stratified squamous epithelium very similar to the epithelium of the skin and vagina. Zeller<sup>6</sup> in 1885 fully discussed this condition. At this time it was customary to treat various uterine disorders by intrauterine applications of caustics such as iodine and formaldehyde. In those patients treated intensively, the entire uterine mucosa became firm and epidermal in character. Fifty per cent of his patients in whom the endometrium had been replaced by squamous epithelium had received such treatment. He expressed the opinion that chronic irritation played an important role in initiating the change from columnar to squamous epithelium in the endometrium.

Mainzer<sup>7</sup> also noted squamous epithelium in the uterine cavity following formalin vaporizations. Squamous epithelium has been found in gonorrheal endometritis (Wertheim and Menge<sup>8</sup>), in endometrial tuberculosis (von Franque<sup>9</sup>), and in pyometra. It is common knowledge that the endometrium of the everted uterus may be replaced by squamous epithelium (Ries<sup>10</sup>). Fluhmann<sup>11</sup> described epidermalization in the cervix and in cervical polyps. In his entire series of 59 cases in which this occurred in the cervix, there were definite signs of chronic irritation. Therefore, he stated that the phenomenon occurred in the adult as the result of chronic irritation in the form of an inflammatory reaction. Various hypotheses have been offered to explain this replacement of columnar by squamous epithelium in the uterus.

It has been suggested that the squamous epithelium may be an ingrowth from the basal layer of normal adjacent squamous epithelium, the extension taking place along the trellis furnished by the gland framework. However, this would not explain the occurrence of squamous epithelium at the tip of a glandular mucous polyp of the endocervix in which there is an isolated nest of squamous epithelial cells at the tip, but where the rest of the polyp including the base is covered by columnar epithelium. Neither does this explain the presence of squamous cell carcinoma in the uterine fundus in which there is no connection with the squamous epithelium of the cervix.

Meyer<sup>12</sup> has shown that, during the third or fourth month of intrauterine life, the squamous epithelium extends high into the cervical canal. At the sixth month, columnar epithelium grows down replacing this and gives the histologic picture usually seen in the adult cervix. Meyer postulated that in this transition basal cells are left beneath the glandular epithelium. At a later date, there is a weakening of the cylindrical cell lining and the rests of basal cells begin to proliferate, producing a squamous epithelial lining.

Another explanation for the presence of squamous epithelium in these locations is that they originate in cellular rests. The genital tract is formed by the fusion of the Müllerian cords (Graves<sup>13</sup>). Thus, the membrane lining the entire canal has a common origin and constitutes the so-called "Müllerian epithelium." The Müllerian epithelium is not uniform in its final development but takes on specific modifications in each of the organs of the genital tract to meet different functional requirements. In the vagina and vaginal portion of the cervix it assumes an epidermal form much like that of the skin, while in the endocervix, the epithelium becomes high and columnar similar to that of the intestines and secretes a true

mucus. Here, it dips down into complicated racemose glands. In the cavity of the uterus the epithelium becomes ciliated, low, and cylindrical; it forms into simple tubular glands that secrete a thin albuminous substance. In the tubes the epithelium is more richly ciliated, low, and nonglandular and covers the delicate rugae that line the tubal lumina. Since the entire system is formed from a common progenitor, the advocates of this hypothesis hold that these undifferentiated cells may remain in adult life and later might produce a squamous type of epithelium.

Such a hypothesis requires the identification of such cellular rests in the endocervix and uterine fundus. Meyer<sup>12</sup> found certain small cells beneath the cylindrical epithelium of the cervix, which he interpreted as representing the rests of basal cells from squamous epithelium that previously covered that region of the cervix. Krompecher<sup>14</sup> maintained that the cylindrical epithelium had an undifferentiated basal layer capable of forming epithelium. Schmidt<sup>15</sup> in studying regeneration of cylindrical cells in the cervix attached considerable importance to certain round cells which he found in profusion in rapidly growing polyps and in erosion. He expressed the opinion that these cells played an important role in regeneration and were not wandering cells or leucocytes.

A direct implantation of squamous epithelium by contact has been suggested by some, as an explanation for the occurrence of squamous epithelium at the tip of a glandular endocervical polyp. Reis<sup>10</sup> spoke of a "sort of infection with pavement epithelium brought about by contact with organs covered with the same variety of epithelium."

Another explanation that has been suggested is that the squamous and glandular tumor cells have arisen from different epithelium, the two tumors developing simultaneously and becoming intimately mixed ("doppel tumor" or "collision tumor"). Kaufmann<sup>16</sup> reported a case of mixed cell carcinoma of the uterine body which he concluded arose from the simultaneous malignant proliferation of the thickened metaplastic surface epithelium and of the glandular epithelium.

A genuine metaplasia of epithelium has been offered as the explanation for the changes in the cervix and uterine body. Kettle<sup>17</sup> has called attention to the polymorphism of the malignant epithelial cell and Herxheimer<sup>18</sup> as early as 1907 expressed the opinion that in mixed squamous cell carcinoma and adenocarcinoma, a single parenchyma was present, developed from an undifferentiated embryonic foundation capable of differentiation in two directions. It has been implied by some investigators that the squamous epithelial cell originates directly from the columnar cell. However, Broders<sup>2, 4</sup> has felt that the columnar cell is differentiated and cannot produce a squamous epithelial cell, but rather that the regenerative cell has the inherent capacity of producing either a glandular or secretory type of cell or a squamous or protective type of cell. Murray<sup>19</sup> has offered adequate experimental proof that the power to differentiate either into squamous cells or glandular cells resides in the regenerative cell. He succeeded in producing squamous cell carcinoma and adenocarcinoma by transplants of a mixed cell tumor from the left axilla of a mouse.

#### METHOD OF STUDY

All mixed adenocarcinoma and squamous cell carcinoma of the uterus seen at the Mayo Clinic from Jan. 1, 1915, to May 31, 1938, inclusive, constituted the material for study. Several blocks of tissue were taken from various portions of the tumor in those cases in which hysterectomy had been performed. Permanent sections were then made by the frozen section technique and stained with hematoxylin and eosin. In a few cases, especially where there was doubt as to the presence of glandular elements in the carcinoma, a mucous stain was done. Biopsy material alone was available in some of the cases. In these, the original mounted microscopic sections were used.

In cases in which hysterectomy had been performed, the extent of the growth in the uterus was determined by frozen sections stained with

Terry's polychrome methylene blue. The case histories were then carefully analyzed so that the clinical course in these patients could be compared with the course in pure squamous cell carcinomas of the cervix and in pure adenocarcinomas of the body of the uterus.

#### INCIDENCE

Mixed adenocarcinoma and squamous cell carcinoma of the uterus is a relatively rare tumor. Only 28 proved cases have been seen at the Mayo Clinic in twenty-five years. Eleven of these occurred in the body of the uterus and 17 in the cervix. They constituted approximately 1 per cent of the total number of uterine carcinomas seen during this period.

#### AGE

The age incidence of patients with this type of tumor is shown in Table I. As is apparent the greatest number of cases fall in the same age groups as do the ordinary cellular types of carcinoma of the uterus (Bowling and Fricke,<sup>20</sup> Norris and Dunne,<sup>21</sup> Healy,<sup>22</sup> Goldstine<sup>23</sup>); 70.6 per cent of mixed cell carcinomas of the cervix and 72.8 per cent of mixed carcinomas of the uterine body occur between the ages of forty and sixty years. The mixed cell tumors of the uterine body occurred in a slightly older age group than those in the cervix, as might be expected (Davis,<sup>24</sup> Donald and Shaw,<sup>25</sup> Healy and Cutler,<sup>26</sup> and Kelly<sup>27</sup>), the average ages being, respectively, fifty-five and fifty-one years. This corresponds closely to the usual age of occurrence of squamous epithelioma of the cervix and adenocarcinoma of the body of the uterus. The youngest patient in the series was 29 years old and the oldest 70 years; in both of these the neoplasm was located in the cervix.

TABLE I. AGE INCIDENCE OF MIXED ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA OF UTERUS

AGE, YEARS	TOTAL		CERVIX		BODY	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
20-29	1	3.6	1	5.9	0	0
30-39	0	0	0	0	0	0
40-49	11	39.3	7	41.2	4	36.4
50-59	9	32.1	5	29.4	4	36.4
60-69	6	21.4	3	17.6	3	27.2
70+	1	3.6	1	5.9	0	0
Total	28	100.0	17	100.0	11	100.0
Average age	53 years		51 years		55 years	

In review of the literature, one is led to believe from reports of isolated cases that the so-called adenoacanthoma of the uterine body occurs much later in life than does the ordinary adenocarcinoma of the body of the uterus. This has led many to subscribe to the hypothesis that the mixed type of neoplasm originates in an area of senile leucoplakia in which the glandular epithelium is replaced by squamous epithelium. However, in this series there seems to be little difference between the age of occurrence of the mixed adenocarcinoma and squamous cell carcinoma and that of the usual adenocarcinoma of the corpus uteri.

In this group there was only a slight difference in the number of full-term deliveries in cases of malignant lesions of the cervix and the body of the uterus. The average number of deliveries was 1.0 in these individuals in whom mixed cell carcinoma of the uterus subsequently developed, and 2.5 in those in whom mixed cell carcinoma of the cervix subsequently developed.

It is interesting to note that six patients (35 per cent) with mixed adenocarcinoma and squamous cell carcinoma of the cervix had symptoms suggesting the menopause at the time of the original examination, while 10 (59 per cent) were in the postmenopausal state. Bowling and Fricke<sup>20</sup> in an analysis of 214 cases

of routine carcinoma of the cervix found that more than 50 per cent of their cases occurred after the menopause while in 20 per cent of the cases the disease occurred before the age of the menopause; thus less than 30 per cent occurred during the menopause. In the mixed adenocarcinoma and squamous cell carcinoma of the body of the uterus, 9, or 82 per cent, occurred after the menopause. This establishes mixed tumors of the uterine body as a postmenopausal disease.

#### SYMPTOMS AND SIGNS

One of the so-called cardinal triad of symptoms (Miller<sup>28</sup>), namely, bleeding, leucorrhea, and pain, was offered as their chief complaint (Table II) by practically all of the patients in this group. These symptoms do not differ from those found in routine carcinomas of the uterus.

TABLE II. CHIEF COMPLAINTS OFFERED BY PATIENTS WITH MIXED ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA OF THE UTERUS

CHIEF COMPLAINT	CERVICAL CARCINOMA		UTERINE CARCINOMA	
	NO.	PER CENT	NO.	PER CENT
Abnormal vaginal bleeding	8	48	6	55
Leucorrhea	4	23	2	18
Abdominal pain	4	23	3	27
Others	1	6	0	0
Total	17	100	11	100

On examination of these patients, it was found that in 64 per cent with mixed squamous cell carcinoma and adenocarcinoma of the cervix the carcinoma had infiltrated the parametrial tissue, whereas in those of the fundus only one had obvious metastasis although two others were considered inoperable because of extension of the growth.

#### TREATMENT

Radium was applied to the cervix in all 17 cases in which the cervix was the site of the carcinoma. In 5 instances it was used as an adjunct to total abdominal hysterectomy; in 11 instances it was supplemented by roentgen therapy. Three of the 5 hysterectomies were of the Wertheim type. In 9 patients in whom the lesion was located in the uterine fundus, hysterectomy was done. Seven of these were abdominal hysterectomies, and 2 were performed by the vaginal route. In 7 cases the hysterectomy was supplemented by roentgen therapy. In 3 cases radium alone was used because of the inoperability of the lesion.

#### COMPLICATIONS TO TREATMENT

In one patient receiving limited irradiation for carcinoma of the cervix, pelvic peritonitis and pneumonia developed. Uremia occurred in 2 patients in whom the Wertheim type of hysterectomy was carried out for carcinoma of the cervix. Rather severe cystitis developed in one patient receiving a complete course of irradiation for carcinoma of the body of the uterus.

#### RESULTS

Of the patients with mixed adenocarcinoma and squamous cell carcinoma of the cervix, 13 were treated five years or more ago, while 7 of the 11 patients with mixed cell carcinomas of the uterine body were treated during this period. Twenty-three per cent of the patients with carcinomas of the cervix who could be traced and 85 per cent with carcinomas of the fundus survived five years or more. Bowing and Fricke,<sup>29</sup> in reviewing 1,491 cases of carcinoma of the cervix, had a five-year survival rate of 26.8 per cent. Stacy,<sup>30</sup> in 215 cases of carcinoma of the body of the uterus of all grades, found that 59.53 per cent were living five years or more following operation.



## PATHOLOGY

*Grade.*—All of these tumors were graded on a basis of 1 to 4 according to the classification laid down by Broders.<sup>2, 31-33</sup> As may be seen from Table III, 83 per cent of the carcinomas of the cervix were Graded 3 or 4 and 11 per cent were Graded 1 or 2, whereas 82 per cent of the carcinomas of the body of the uterus were Graded 1 or 2. These percentages are in fairly close agreement with those usually given for ordinary carcinomas of the cervix (Bowling<sup>29</sup>) and of the body of the uterus. In only two cases was there a mixture of grades in the same tumor. One of these occurred in the cervix proper and the other in the uterine body. Both of these tumors were Graded 3 as to the squamous cell carcinoma and 2 as to the adenocarcinoma.

TABLE III. GRADES OF MIXED ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA OF THE UTERUS

GRADE	CERVIX		BODY	
	NO.	PER CENT	NO.	PER CENT
1	0	0	1	9
2	2	11	8	73
3	10	59	1*	9
4	4	24	0	0
2 grades	1†	6	1‡	9
Total	17	100	11	100

\*Mixed adenocarcinoma and squamous cell carcinoma Grade 3 at internal os and Grade 1 adenocarcinoma in left horn of the uterus.

†Grade 2 adenocarcinoma and Grade 3 squamous cell carcinoma of the cervix.

‡Grade 2 adenocarcinoma and Grade 3 squamous cell carcinoma of the uterine body.

One case is of particular interest in that the uterus contained two separate carcinomas, a Grade 1 adenocarcinoma in the left horn of the uterus and a Grade 3 mixed squamous cell carcinoma and adenocarcinoma at the internal os. This case has previously been reported by Counseller and Butsch.<sup>34</sup>

*Location and Extent of the Carcinoma.*—In the 14 cases in which the uterus was available, an attempt was made to determine the extent of the lesion in the uterus by numerous blocks of tissue taken from the margin of the tumor and cut by the frozen section technique. Of the 14 specimens studied, the primary carcinoma was considered endocervical in 5 cases and fundal in 9 cases. In the entire series there were only 2 cases in which there was doubt as to whether the carcinoma should be considered as cervical with invasion of the body of the uterus or fundal with invasion of the cervix. In these cases the opinion of the pathologist who saw the fresh specimens was taken. One of the doubtful cases was considered by the pathologist as originating in the cervix and the other in the body of the uterus.

The cervical carcinomas varied in size from a lesion measuring 1 cm. by 1 cm. by 1 mm. to one involving the entire cervix and body of the uterus. The smallest carcinoma of fundal origin measured 3 by 3 by 2 cm; the largest involved the entire endometrium.

*Relative Amounts of Squamous and Adenomatous Element in the Tumor.*—A review of the several slides on each specimen was undertaken to estimate whether the adenomatous or squamous element was in the majority throughout the tumor. In the cervical carcinomas, the adenomatous or squamous elements predominated in approximately an equal number of cases (Figs. 1 and 2), the squamous element being in the majority in 9 tumors and the glandular in 8 tumors. On the other hand in the entire 11 cases of carcinoma of the body of the uterus, the adenomatous element was predominant (Fig. 3).

*Associated Neoplasms.*—Leiomyomas of the uterus were frequently associated with the carcinomas in this series. In 4 of the 5 cases in which hysterectomy had been performed for carcinoma of the cervix, leiomyomas were demonstrated in the uterine musculature. In one other case supravaginal hysterectomy had been performed six years previous to the occurrence of the carcinoma of the cervix because of leiomyoma. In 5 of the 9 patients who had had hysterectomy for carcinoma of the body of the uterus, leiomyomas were also present.

## COMMENT

It can be seen that the symptoms, rapidity of growth as measured by the grade of malignancy, and prognosis of mixed squamous cell carcinoma and adenocarcinoma of the uterine cervix do not differ appreciably from those of ordinary squamous cell carcinoma in the same location. Similarly mixed adenocarcinoma and squamous cell carcinoma of the uterine fundus does not differ materially from adenocarcinoma of the fundus.

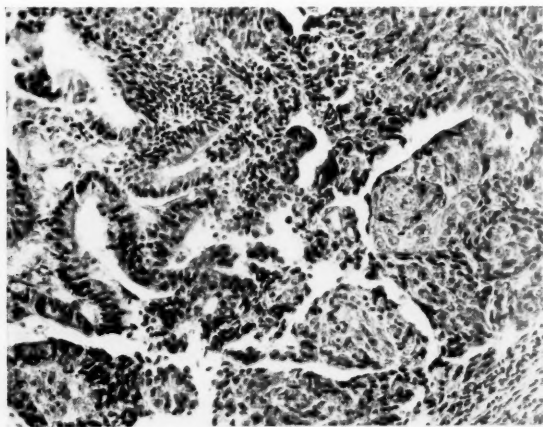


Fig. 1.—Mixed squamous cell carcinoma and adenocarcinoma of the cervix. The squamous cell carcinoma is differentiating into pearls (hematoxylin and eosin  $\times 170$ ).



Fig. 2.

Fig. 2.—Mixed adenocarcinoma and squamous cell carcinoma of the cervix. There is a small island of squamous cell carcinoma (hematoxylin and eosin  $\times 95$ ).



Fig. 3.

Fig. 3.—Mixed adenocarcinoma and squamous cell carcinoma of the uterine body (hematoxylin and eosin  $\times 70$ ).

It is impossible to make a positive assertion concerning the origin of the mixed squamous cell carcinoma and adenocarcinoma of the uterus. It would appear most likely that it originates from a regenerative type of epithelial cell which is capable of forming either benign or malignant, squamous or glandular epithelial cells. Squamous epithelium has been demonstrated in the fundus of the uterus. Not infrequently small islands of squamous epithelium are found in glandular polyps arising from the region of the endocervix (Fig. 4). However, carcinomas can rarely be demonstrated as arising in such benign metaplastic epithelium. Furthermore, in none of the cases of mixed squamous cell carcinoma



Fig. 4.

Fig. 4.—Polyp arising from endocervix. There is a transition of columnar epithelium to benign squamous epithelium (metaplasia) (hematoxylin and eosin  $\times 120$ ).

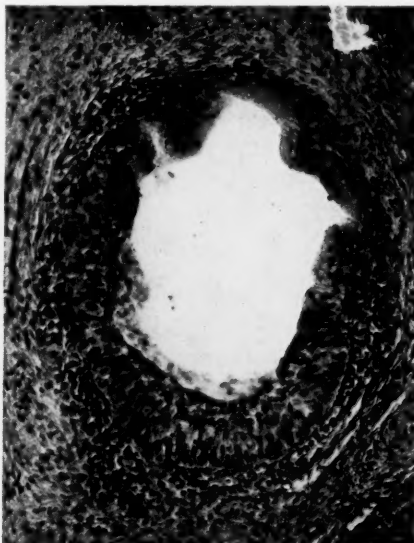


Fig. 5.

Fig. 5.—Squamous cell carcinoma of the endocervix. The acinus lined by squamous cell carcinoma on one side and benign columnar epithelium on the other (hematoxylin and eosin  $\times 165$ ).

and adenocarcinoma of the fundus of the uterus could benign squamous epithelium be found in the endometrium. It would appear that the malignant squamous cells in mixed cell carcinomas of the uterus originate from glandular epithelium without the formation of benign squamous epithelium (Fig. 5).

#### SUMMARY

Twenty-eight cases of mixed adenocarcinoma and squamous-cell carcinoma of the uterus have been described. Eleven of these were located in the body of the uterus and 17 in the cervix. They form approximately 1 per cent of the entire group of uterine carcinomas. The symptoms and signs do not differ appreciably from those of the more common varieties of carcinoma found in the uterine fundus and cervix. Eighty-three per cent of the mixed adenocarcinoma and squamous cell carcinoma

of the cervix were Graded 3 and 4, according to Broders' classification, whereas 82 per cent of the carcinomas of the uterine body were Graded 1 and 2. In mixed cell carcinomas of the cervix neither glandular nor squamous cell elements predominated, whereas the adenomatous element was predominant in all cases of carcinoma of the body of the uterus.

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## PUBIOTOMY IN IMPACTED MENTUM POSTERIOR PRESENTATION

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THE purpose of this paper is to report a case of impacted posterior face presentation, treated successfully by pubiotomy, and to review the subject with the idea of re-emphasizing the procedure as a method of treating impacted face presentation not suitable to any other form of treatment.

If the chin rotates anterior, as it does in the majority of cases, delivery usually can be accomplished through the birth canal, spontaneously, or by the judicious use of forceps. But with partial extension of the head and with the chin posterior the forehead reaches the pelvic floor first and rotates to the front.

Continued labor causes the presenting part to descend until the head, neck, and chest of the child are firmly impacted in the pelvic cavity. Further progress is impossible and death of the child and subsequent rupture of the uterus are likely, unless some suitable operative interference is instituted at once. This picture presents a most serious complication.

If the presentation is diagnosed before the engagement of the face, changing of the presentation may be tried or the maneuver of Schatz, Baudeloeque, or Playfair-Partridge attempted. If conditions are suitable, version may be done. Cesarean section may be accomplished in most cases with excellent results.

Unfortunately these patients usually have been allowed to progress in labor until impaction has resulted. The membranes have ruptured hours before, and there have been attempts at delivery. Under these circumstances there are a limited number of procedures which recommend themselves as far as the safety of the mother and baby is concerned.

Low segment cesarean section would be difficult, as trouble is often encountered in a normal presentation in extracting the head when engagement has occurred. Such a procedure in impacted face presentation would be most difficult. The limited mobility of the presenting part and the necessary application of forceps from the occiput to the mentum would not facilitate easy extraction, and dragging the head from deep in the pelvis would court injuries to the child. Extension of the incision above the bladder reflection would defeat the purpose of the operation.

Extraperitoneal section would present similar difficulties besides being a far more formidable procedure.

The treatment usually suggested in the late editions of our standard textbooks for impacted face presentation is low segment cesarean section or craniotomy if the child is dead or dying. There is bare mention of pubiotomy.

Recent advances in the technique of cesarean section have narrowed the indications of pubiotomy to a limited field.



A. H. Morse, 1912, reported a case so treated and found four more in the literature. He discusses these cases in detail with an analysis of each, besides his own, which terminated successfully with a live baby and mother. The first to do the operation for this complication was E. G. Montgomery, of Quincy, Illinois, who, in 1894, performed extramedian symphysiotomy. The child was delivered but died twenty minutes later from asphyxiation.

The second case he reported was in Leopolds Clinic by Kannegeiser, which ended fatally for the child. The baby was delivered by craniotomy. The conjugate vera in this case was estimated at only 7.25 cm.

The third and fourth were by O. Pankow in 1910. In Pankow's first case the diagnosis was face presentation posterior in a primipara. Twenty-seven hours had elapsed between rupture of the membranes and the operation. Open pubiotomy was performed and the patient was allowed to deliver herself four hours later. She suffered high fever with streptococcic endometritis, thrombosis of the left and right legs. The patient was discharged on the sixty-seventh day after a stormy convalescence.

Pankow's second case was in a primipara. Open pubiotomy again was done. Eight and one-half hours later the baby was delivered with forceps, was deeply asphyxiated and could not be revived. The patient was discharged on the twenty-fourth day.

Titus credits Morse with saying that Montgomery's case would have had a happier ending had the child been in better condition at the outset, and that Kannegeiser's patient had a conjugate vera of 7.25 cm. and the delivery would have been difficult with a normal presentation.

In Pankow's cases open pubiotomy was used, which, Morse says, according to Titus, is more likely to infection, as an open wound in the region of genitalia is present. Waiting eight and one-half hours before delivery probably contributed to the injury and asphyxiation of the child in the second case.

Titus, 1916, reviewed Morse's paper, added his own case, and found reference to two more in the literature, one by Jacobsen and another by Whitridge Williams, reported in his textbook with no detailed history.

Jacobsen's patient was a large primipara, in labor for thirty-six hours with a posterior face presentation. The child was in good condition. The open pubiotomy was performed, but a vesicovaginal fistula developed. The patient was discharged with her baby after a troublesome convalescence; her fistula not quite healed.

Titus' patient, a para vi, appears to be the eighth treated in this manner, with face firmly impacted and the chin posterior. Pubiotomy by Doederlein technique was done on the right side and delivery was effected with the chin still posterior. The child was asphyxiated but breathed readily upon resuscitation. There was no laceration or bladder injury. The puerperium was febrile and this was attributed to the pubiotomy wound, but later it was discovered that the patient had an active pulmonary tuberculosis. She suffered no disability from the operation and was released after thirty-nine days. The baby weighed seven pounds upon discharge.

I was able to find only one other case in the literature.

In 1927, M. M. Audibert and Galy Gasparrou reported a case of pubiotomy done by them for impacted posterior face presentation. The history of their case follows: A primipara, 30 years of age, normal size, entered the Obstetrical Clinic, September, 1927, was at term and had been in labor for fifteen hours. The face was engaged in right mentum posterior. Dilatation was 2 or 3 cm. Next day the membranes ruptured. There was dilatation 4 to 5 cm., and great edema of the cervix. Contractions were strong and regular. Morphine, 0.01 Gm., was given without results.

Under spinal anesthesia a saw was passed on the left side after the technique of Doederlein. There was a median anterior and posterior incision of the cervix. Forceps were applied and the face easily brought to right transverse, but here no further progress could be made. It was decided not to sever the pubis until there had been many attempts to deliver with forceps.

A male child was born after pubiotomy but died seven hours later. The autopsy showed cranial injuries. The patient was discharged on the thirteenth day, walked without difficulty, and had no diastasis of sacroiliac joints.

The report of my case, which appears to be the tenth treated in this manner, follows:

Mrs. E. S., aged 30 years, primipara, entered St. Vincent's Hospital, May 23, 1938. Dr. R. A. Bissett, her physician, saw her early in the morning of May 24, made the diagnosis of posterior face presentation, and called me at 8:30 A.M. for consultation. She had been in labor thirty hours. He had made no attempts at delivery, but the patient's temperature was 100° F., and her pulse was 110, on admission.

She had been in labor at home all the preceding day, the membranes having ruptured before the onset of labor. At this time her pains were strong and regular, and there was some evidence of a contraction ring about 10 cm. above the pubis. The patient was exhausted.

The fundus measured 38 cm. The breach was in the fundus. The fetal heart was on the right side, midway between the umbilicus and anterior superior spine of ilium. The presenting part was fixed in the pelvis. The pelvic measurements were: Interspinous, 26 cm.; intercrural, 31 cm.; external conjugate, 21.5 cm.; introchanteric, 34 cm.; bischial, 10 cm.; anteroposterior, 12 cm. The promontory could not be reached because of the presenting part.

Vaginal examination showed the cervix to be fully dilated and retracted. The face was presenting with the chin posterior to the right and well below the ischial spines. An unsuccessful attempt was made to dislodge the child, but not even the slightest mobility could be obtained with moderate upward pressure. It was evident that the face was firmly impacted. Nevertheless forceps were applied and an attempt made to rotate the head, so that the chin would be anterior.

A moderate amount of force was applied without producing the slightest tendency toward rotation. At this time a one-inch incision over the spine of the pubis was made. The superior border of the pubis was exposed on the left side. There being no pubiotomy needle available, it was necessary to use a large aneurysm needle. After catheterization, the finger-guided needle was passed back of the pubis. The left labium was pulled toward the center so that the point of the needle would emerge through the skin. A Gigli saw was threaded through the wound, beneath the pubis, and the bone was severed. A deep left lateral episiotomy was performed.

Assistants held the patient's legs on either side, making counter pressure so that the weight of the thighs would not cause too much separation of the bone ends. The separation obtained was 2 to 3 cm. Kielland forceps were applied and rotation was accomplished with considerable difficulty. The face was then delivered as a right mentum anterior. The baby boy showed no signs of asphyxia and breathed immediately. Its weight was 3,410 Gm. The patient showed considerable shock after the delivery. Her pulse was 130, weak, and thready. She was given 1000 c.c. of 10 per cent glucose, intravenously. There was no extension of the episiotomy wound and catheterization showed clear urine. A retention catheter was inserted and episiotomy and pubiotomy wounds were sutured without drainage. The pelvic girdle was strapped with eight-inch adhesive tape and the patient was placed in bed in a pelvic swing. Her pulse was 120 and temperature 100° F. until the eleventh day post partum. Some dark, sticky urine passed through the catheter on the first and second days, but the urine soon became normal in appearance.

On the seventh day, there was a small opening in the episiotomy wound, from which there was a purulent discharge. The wound healed by the twelfth day. The patient was allowed to be in a chair on the twenty-first day post partum. She walked on the twenty-third day with no limp and no disability. She was discharged from the hospital the same day. The baby was apparently normal, weighing 3,715 Gm. Although the head was still extended backwards as in the position at birth, it was freely movable, but tended to resume the backward position. At the end of two months this condition had remedied itself. The patient at the end of six months had no apparent disability from the pubiotomy.

## DISCUSSION

From observation of my own case, and reviews of cases I have found in the literature, it can readily be seen that these patients are poor surgical risks and pubiotomy lends itself admirably to their treatment. It is certainly unfair to condemn pubiotomy on its maternal and fetal mortality when its indications have been narrowed to the poorest of surgical risks. Guggenberger gives statistics in his treatise on face presentation and lists maternal and fetal mortality under all treatments in 47 operative cases. Sixteen cesarean sections were done with three maternal and two fetal deaths. Two of these sections were transperitoneal, and the patients died from peritonitis. One was extraperitoneal and the patient died from generalized sepsis. One pubiotomy was done in this series, which was successful for mother and baby.

In all of the 10 cases here reviewed for impacted posterior facial presentation, there has not been a single maternal death, though the fetal mortality is 50 per cent. This fetal mortality might have been reduced considerably had three of the patients not been allowed to deliver themselves spontaneously after pubiotomy.

We have been taught that posterior face presentation should be allowed to progress in labor, anterior rotation of the chin should be awaited to permit spontaneous delivery, and, failing in this, vaginal manipulations to change the presentation should be tried.

We also have been instructed that the mortality of the various types of cesarean section is increased in direct proportion to the length of labor and to the number of vaginal manipulations.

In view of all this, we must accept the operation of pubiotomy as an emergency procedure when the child is alive. It is more simple, less shocking and carries a lower maternal mortality than the former operation of any type in this condition. Between craniotomy and pubiotomy there can be no choice, as maternal mortality statistics alone would support the latter procedure.

It is not my wish to advocate pubiotomy in competition with low cervical cesarean section, but I do believe that pubiotomy has a definite indication in posterior impacted face presentation. The two procedures have no common indications. Only those cases unsuitable for cesarean section come into the pubiotomy category.

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## TUBAL PREGNANCY ASSOCIATED WITH TUBAL TUBERCULOSIS

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**N**OTWITHSTANDING the belief that various sequelae of tubal inflammation are the most common causes of pregnancy within the Fallopian tube, the combination of tubal tuberculosis and tubal gestation is comparatively rare. In an exhaustive study of the literature, both domestic and foreign, I found, as outlined in Table I, only 32 cases of the dual condition recorded. This would seem to indicate quite clearly that, as a cause of extrauterine pregnancy, tuberculous disease of the Fallopian tubes is seldom responsible.

In a study of 55,000 surgical specimens in the laboratories of The Jefferson Medical College Hospital, from 1907 to 1939 inclusive, there were recorded 209 cases of tubal gestation. In none of these was tuberculosis observed. There were also recorded 38 cases of microscopic tuberculous salpingitis.

For the eleven-year period, from 1928 to September, 1939, inclusive, there were operated upon in the hospital 193 cases of various forms of extrauterine pregnancy or nearly 20 cases each year. None of these showed any evidence microscopically of tuberculous infection of the tubes.

Moreover, in a fairly active gynecologic practice extending over a period of many years, the clinical record herewith presented outlines the first case histologically demonstrated which I have thus far encountered.

The clinical and pathologic history of the patient whom I studied, bringing the total number thus far recorded to 33, is as follows:

Mrs. W. K. (CH-1079), aged 30 years. The family history is entirely negative for hereditary disease. The parents of the patient together with all sisters and brothers (4 sisters and 3 brothers) are living and well.

The patient has never had any serious disease. Her menstrual function was established at twelve, always regular, every thirty days, the flow lasting from four to five days, moderate in amount. At times it has been accompanied by slight pain. The last normal period occurred about May 1, and the preceding period thirty days previously.

The patient was first married at the age of 17. Two years later she gave birth normally to a full-term female child. There were no post-partum complications. She was married again at the age of thirty.

*Present Trouble.*—The patient was admitted to The Jefferson Medical College Hospital on the afternoon of July 3, 1939. She was discharged well on July 22, 1939.

Two weeks before coming under observation she experienced some uterine bleeding of a mild type. This was associated with considerable pelvic distress, and she believed the symptoms indicated an oncoming miscarriage. She was seen by her family doctor who made a tentative diagnosis of an incomplete abortion and, accordingly, admitted her to the Mercer Hospital, Trenton, N. J., for treatment. Shortly after her admission a therapeutic curettage was performed. She remained in the hospital for five days.

Following her dismissal from the hospital the bleeding recurred and continued "off-and-on" until she was admitted to the Jefferson Medical College Hospital on July 3. At this time, in addition to the uterine bleeding, she was suffering from severe pelvic pain. This was intensely aggravated during a bimanual examination, so much so that the patient developed profound shock.

The abdominal wall was hypersensitive and movement of the cervix was exceedingly tender. The posterior vaginal fornix was distended and almost convex. In the right side of the pelvic cavity an indefinite mass was felt. From the foregoing physical symptoms and signs, a provisional diagnosis of a ruptured tubal pregnancy was made.

TABLE I. VERIFIED CASES OF EXTRAUTERINE PREGNANCY ASSOCIATED WITH TUBAL TUBERCULOSIS

NO. OF CASES	YEAR OF REPORT	AUTHOR	AGE OF PATIENT	MARITAL HISTORY	TUBES PREGNANT	TUBAL TUBERCULOSIS	OUTCOME OF OPERATION
1	1896	Warthin	38	Married 13 years. Sterile	Left	Both tubes	Died tenth day post-operative
2	1898	Freericks	36	Married 6 years. Para iv	Left	Left	Not recorded
3	1900	Alexander and Moskowitz	25	Nulliparous	Left	Left	Recovery
4	1902	Anspach	31	Married 8 years. Sterile	Right	Right	Recovery
5	1904	Stein	24	Nulliparous	Right	Both tubes	Not recorded
6	1906	Resinelli	34	Para iii	Left	Both tubes	Not recorded
7	1910	Ferroni	36	Para iii	Right	Both tubes	Not recorded
8	1911	Falco	24	Nulliparous	Left	Both tubes	Died postoperative
9	1913	Mülsam	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded
10	1915	Bovin	34	Married 9 years. Sterile	Right	Right	Not recorded
11	1916	Kröner	41	Married 11 years	Not recorded	Both tubes	Recovery
12	1920	Müller	28	Para ii	Left	Both tubes	Died third day post-operative (sepsis)
13	1920	Schröder and Rau	41	Married 11 years. Sterile	Not recorded	Both tubes	Recovery
14	1922	Aconci	33	Sterile	Right	Right	Recovery
15	1928	Mossa	34	Married 5 years. Sterile	Right	Left	Recovery
16-19	1931	Martius (4 cases of Steuber)*	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded
20	1931	Höppner	35	Not recorded	Left	Left	Not recorded
21	1932	Werhatzky	31	Not recorded	Right	Both tubes	Not recorded
22	1932	Therkelsen	32	Nulliparous	Right	Right	Died tenth day post-operative
23	1934	Stefanelli	22	Para ii	Not recorded	Same tube	Not recorded
24	1936	Schönberg	26	Not recorded	Right	Right	Recovery
25-26	1936	Tenney	24	Para i.	Left	Left	Recovery
			36	Married 10 years. Nulliparous	Left	Left	Recovery
27	1938	Reifferscheid	37	Married 5½ years. Sterile	Not recorded	Same tube	Recovery
28	1938	Limpach and Boy	32	Married 4 years. Sterile	Left	Left	Not recorded
29	1939	Stevenson and Wharton	37	Married 11 years. Sterile	Left	Both tubes	Recovery
30	1939	Tenney**	40	Married 20 years	Right	Right	Recovery
31	1939	Stein	29	Married 8 years. Nulliparous	Right	Right	Recovery
32	1940	Busby and Fisher	32	Married 5 years. Nulliparous	Left	Left	Recovery
33	1940	Bland†	30	Married 13 years. Para i.	Right	Right	Recovery

\*Details not recorded.

\*\*Personal communication; case not reported in literature.

†Personal case.



Blood examination showed red cells, 3,500,000; white cells, 8,000; and hemoglobin, 75 per cent. The urinalysis was negative, temperature 101° F., and pulse 82.

*Operation.*—Following admission she was immediately prepared for operation. Under gas-oxygen-ether anesthesia a diagnostic curettage followed by a posterior vaginal incision was performed. Through the incision a large quantity of fresh blood immediately escaped from the pouch of Douglas, thus confirming the diagnosis of a ruptured or aborted tubal gestation.

The patient was then placed in a modified Trendelenburg position and a mid-line incision was made. The abdominal cavity was inundated with fresh blood, and a large retortlike mass was found in the right side of the pelvis. This was delivered through the abdominal incision and resected. It was found to be a well-advanced tubal pregnancy, undergoing abortion. The left ovary and tube were examined, but were grossly not abnormal. The abdominal incision was closed, and



Fig. 1.—Illustration of tuberculosis and pregnancy in the same Fallopian tube. The upper half, A, illustrates the portion of the tube containing the tuberculosis; and B, illustrates a portion of the tube containing the products of conception.

during closure, the patient received 300 c.c. of blood intravenously. This was repeated the following day and two days subsequently. During the first forty-eight hours, the condition of the patient was somewhat disquieting, but after that her recovery was wholly uneventful.

*Follow-up Record.*—Since her dismissal from the hospital, she has greatly improved. An x-ray of her chest made on Dec. 5, 1939, did not disclose any evidence of tuberculous disease, showing clear apices and normal peribronchial lung fields.

*Pathologic Report.*—*Specimen:* (Dr. Carl Bucher) Right Fallopian tube, ovary, and curettings. In diameter the Fallopian tube measured 6 cm. at the proximal end and gradually enlarged toward the distal end to form a dark, solid mass. The interior was mainly spongelike in consistency. There was no evidence of a true placenta or fetal structures. The ovary measured 3 by 2 by 2 cm. It was grayish in color and on section many small cystic cavities were observed.

*Histology:* 1. Several sections were taken from the Fallopian tube. The wall of the structure was edematous and hemorrhagic. On the inner surface there was considerable decidual tissue and in the lumen some "bits" of amnion as well as some chorionic villi. In addition, there was marked inflammatory reaction through-

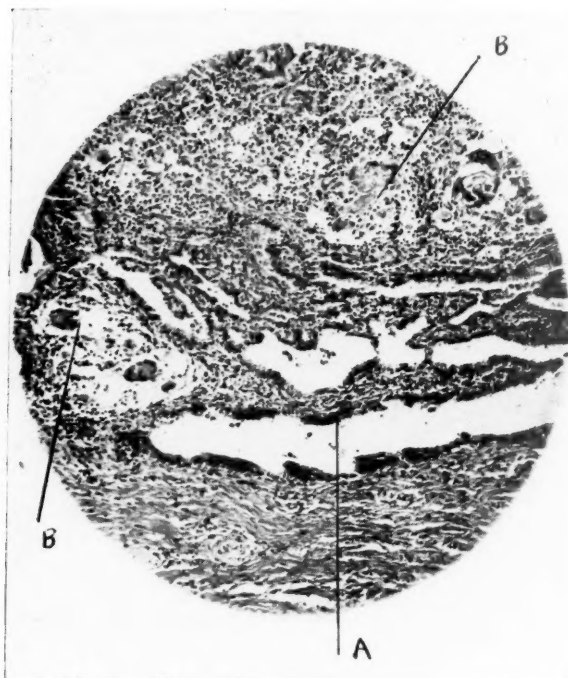


Fig. 2.—Section of a Fallopian tube, illustrating decidual reaction (A) and tubercles (B).

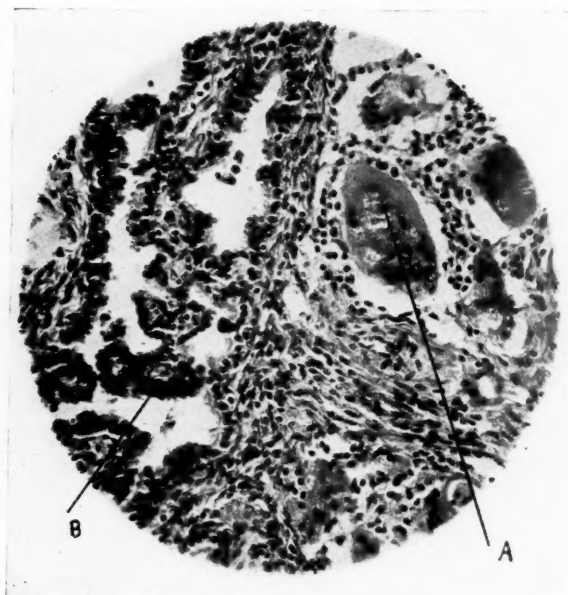


Fig. 3.—High power magnification of a portion of Fig. 2, illustrating a giant cell within a tubercle (A) and decidual tissue (B).

out the tubal wall (Fig. 2). Sections taken from other portions of the tube showed an entirely different picture from that found in ordinary cases of tubal gestation. In these, there was observed extensive edema and hemorrhage together with an inflammatory reaction characterized by infiltration of the round cells. Most of these cells were lymphocytes. In many areas there were characteristic tubercles made up of a proliferation of epithelioid cells, giant cell formation, and an outer zone of inflammatory cells, chiefly lymphocytes (Fig. 3).

2. Sections taken from the ovary disclosed the presence of numerous cysts of varying size lined with low cuboidal epithelium. There was no evidence of tuberculosis in the specimen.

3. A microscopic section of the curetted tissue was made up almost exclusively of blood clots and necrotic material. There was not sufficient tissue to make a positive diagnostic statement.

*Diagnosis.*—(a) Tubal pregnancy, right; (b) tuberculosis of the Fallopian tube, right; (c) cystic ovary, right.

#### COMMENT

With tuberculosis accountable for 10 per cent or more of the cases of inflammatory disease of the uterine adnexa, it would seem logical to assume that pregnancy in the tubes, thus affected, should be more frequently encountered. The rarity of the combined condition is due chiefly, no doubt, first, to the invariably bilateral involvement of the tubes with tuberculous disease, second, to the widespread disorganization of the tubal walls with obstruction of the lumen and, third, owing to the inflammatory reaction in the tubal walls, to the prompt and early occlusion of their abdominal ostia.

Obviously, in cases of this character conception in the tubes is wholly impossible. It is only those cases of a localized type, with the tubal canal still more or less patent, that will permit ingress of the spermatozoa through the uterine and the ova through the fimbrial end and thus permit union to occur.

Finally, the relatively uncommon association of tuberculous salpingitis and tubal pregnancy may be partially explained on the ground that all tubal gestations are not, unfortunately, routinely studied in a microscopic way. If this course were generally practiced, it is likely that many more case histories would find their way into the literature.

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## THE RELATION OF OBSTETRIC COMPLICATIONS TO STERILITY\*

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THE purpose of this paper is to present the results of an investigation to determine the incidence and type of obstetric complications, including abortions, which occurred in 372 patients who have been treated for sterility in the private practice of Dr. C. J. Andrews and myself. All of these patients presented themselves to us with the primary complaint of sterility. Many of them made an inadequate number of visits to the office so that the results of their treatment could not be observed. This study is limited to those patients whose records revealed pregnancy or were followed by us for at least three years. This reduced the total number of cases reported to 118.

It is logical that women who have difficulty in becoming pregnant, provided the cause is not obvious, would possess certain inherent qualities which would affect the normal course, development, and delivery of their offspring. The normal physiology of the endocrine system is so delicately interrelated that maladjustments in its function produce alterations in the physiology, metabolism and growth of the woman to the extent that it is reflected in the shape of the pelvis, the maturation of the ovum, the production of secondary sex characteristics, the size of the uterus, tubes, and vagina, and upon the ovarian and pituitary secretions so necessary for the maintenance of pregnancy.<sup>1</sup> During pregnancy all of the endocrine organs are functioning at their highest efficiency and at delivery their climax is reached. Failure or partial failure in one or a combination of these factors either during pregnancy or at delivery may result in clinical manifestations, such as uterine inertia, post-partum hemorrhage, and premature separation of the placenta.<sup>1</sup> Experimental and clinical evidence is accumulating which points to endocrine dysfunction as a cause of pre-eclampsia and eclampsia.<sup>2, 3</sup> Endocrine imbalance may make itself evident in the type of pelvic conformity which would result in various degrees of cephalopelvic disproportion, arrested descent of the head, posterior position, breech presentation and transverse lie.<sup>1</sup>

For years ectopic pregnancy has been prominent as a complication in those patients who found it difficult to become pregnant.<sup>4</sup> Ectopic pregnancies may have many causes, including damaged lumen of the oviducts, or underdevelopment of the lumen resulting from endocrine imbalance.

### MATERIAL

Of the 118 patients studied, 9 aborted spontaneously and are listed separately, leaving 109 to be studied as to their obstetric complications. These 109 patients have been divided into two age groups: Those between twenty-one and thirty years

\*Read at a meeting of the Norfolk County Medical Society, March 25, 1940.

and those between thirty-one and forty years. There are 70 patients in the first group of whom 32 became pregnant and were delivered while 38 failed to become pregnant. Of the 32 who were delivered, twelve patients encountered an obstetric difficulty as listed in Table I. In the second age group, there were 39 patients of whom 16 became pregnant and were delivered while 23 failed to become pregnant. Of the 16 delivered, 7 encountered obstetric difficulties as shown in Table I.

To summarize, 372 case records were examined. Of these, 118 patients were studied, 9 aborted, 48 came to delivery, and 61 failed to conceive. Of the 48 delivered, 19, or 39.5 per cent, encountered major obstetric difficulties. Including abortions 57 conceived. If the abortions were added to the complications, it would increase the total number of complications to 28 or 49 per cent of those who conceived.

TABLE I

AGE	DELIVERED	FAILED	COMPLICATION
31-40	16	23	R.O.P., difficult forceps, stillborn
39 cases			R.O.P., Midforceps, long labor
			L.O.P., Midforceps, long labor
			Midforceps, slow dilatation, long labor
			Abruptio placentae, Porro cesarean
			Ruptured ectopic
			First breech, second central placenta previa, transverse position
	21-30	32	38
70 cases	R.O.P., midforceps, Scanzoni		
	R.O.P., midforceps, uterine inertia, hypertension		
	R.O.P., midforceps, Scanzoni		
	L.O.P., midforceps, moderate disproportion, difficult delivery		
	Ruptured ectopic		
	Ruptured ectopic		
	Placenta previa marginalis		
	Premature labor 7½ mo.		
	Cesarean for disproportion		
	Abruptio placentae, stillborn		
	First ectopic, second disproportion-cesarean, third monster, fourth cesarean		

TABLE II

Total records studied	372	
Case records used	118	
Abortions	9	
Exclusive of abortions	109	
Became pregnant and delivered	48	40.6%
Failed to conceive	61	
Total complications	19	39.5%
Including abortions	28	49.0%

Obviously this study is not of a sufficiently large series to be conclusive but it does suggest:

1. That the obstetrician, in giving prenatal care, must bear in mind the etiologic background of the individual patient's sterility.
2. That obstetric complications have a higher incidence in women who become pregnant following treatment for sterility.
3. That, due to the increased incidence of obstetric complications, expert obstetric judgment at delivery is needed.



4. That more studies are needed for the exact correlation of specific obstetric complications to their related backgrounds of sterility.

5. That these findings should in no way deter the patient's desire for the correction of sterility, but should conversely increase the physician's vigilance in carefully handling any complication that might arise.

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605 MEDICAL ARTS BUILDING

### SUBARACHNOID INJECTION OF ALCOHOL FOR THE TREATMENT OF PAIN IN GENITAL CARCINOMA

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THE importance of the treatment of intractable pain in patients with chronic progressive disease of various kinds is obvious. Since the subarachnoid injection of alcohol has received considerable attention because of the ease of its administration and its reported efficiency, it was decided to evaluate the results obtained from its use at the University Hospitals in patients with malignant disease of the female genitalia.

#### SUBJECTS

During the years 1933 to 1939 inclusive, 29 patients with incurable genital carcinoma received one or more subarachnoid injections of alcohol. The records of 22 were deemed sufficiently complete for the purpose of this study. The carcinoma originated in the cervix in 20, on the vulva in 1, and in the vagina in 1. A total of 27 injections was made, 5 patients receiving 2 treatments.

#### TECHNIQUE

All injections were made at or below the eleventh thoracic interspace, using recently distilled and carefully stored ethyl alcohol with no more than 6 per cent water.

Alcohol is lighter than spinal fluid and will overlie it in a more or less definite stratification. Its action is upon the unmyelinated pain and thermal fibers of the dorsal roots as they emerge from the cord and pass through the subarachnoid space.

During injection, the patient lies on the unaffected side. If the pain is bilateral, treatment must be repeated the following day with the patient lying on the other side. Accurate localization of pain-carrying segments is desirable, so that the initial injection will attack the desired fibers.

A number 19 or 20 gauge, spinal puncture needle is inserted into the subarachnoid space and 7.0 to 10.0 c.c. of spinal fluid withdrawn. Using a tuberculin type syringe, 0.5 to 1.5 c.c. of alcohol are injected during a three-minute interval. Rapid injection, movement of the patient during or shortly after injection, or introduction of air will interfere with the accurate stratification of the alcohol at the planned level. After the injection, the patient lies quietly on the side for sixty minutes and remains in bed for ten hours.

#### RESULTS

Detailed results of injections in the 22 patients in this series are summarized below. Of this group 9 received no or poor relief (lasting less

than seven days), 5 obtained indifferent relief persisting longer than seven days. The remaining 8 patients obtained good relief which lasted well beyond a week.

During injection there was usually a sudden burning sensation which gradually faded into a warm glow over the sensory distribution of the affected roots. Sensory test showed hypalgesia and lesser degrees of hypoesthesia. Transient motor paralyses, sphincter disturbances and loss of the deep reflexes were frequently observed. As the alcohol diffuses into the spinal fluid, it becomes diluted and inactive. The leucocytes in the spinal fluid become temporarily increased, and there is often a mild febrile reaction which persists for twenty-four to thirty-six hours. In certain cases, in spite of adherence to a rigid technique, permanent motor weakness and sphincter disturbances will occur.

Since some of the patients were discharged shortly after receiving the injections, data on the late results were incomplete. Questionnaires were sent to the 10 patients in this group; but replies were received from only 3; 4 had died in the interval.

Eight of the 22 had motor paralysis, 6 had sphincter disturbances, and 5 had combined motor and sphincter disturbances, all of which lasted for more than three days. Five of the 8 with motor paralysis and 3 of the 5 with sphincter disturbances fell into the group of 8 patients who obtained good relief. In contrast, the group of 9 who obtained no or indifferent, transient relief included only one patient with combined motor and sphincter disturbances and one who suffered urinary incontinence.

#### DISCUSSION

To Dogliotti<sup>1</sup> is accredited the first report of subarachnoid injection of alcohol for the treatment of intractable pain. Since this time there have been many reports concerning its use, indications, and results. The various techniques are fundamentally similar. Stern<sup>2</sup> feels that the desirable alcoholic concentration in the spinal fluid is 30 per cent, and it has been established by experience that this is most efficiently achieved by injection of alcohol of approximately 95 per cent concentration by volume. Higher concentrations produce undesirable changes in the cord substance, and lower concentrations are ineffective. The closer to the end of the spinal cord injections are made, the less the volume of alcohol necessary to produce the effect. Below the third lumbar interspace, it is wise not to use more than 0.6 c.c., because at this level the size of the subarachnoid space in relation to the mass of nervous tissue is small and larger amounts affect the cord and give a cauda equina syndrome. This danger exists at any level, but when injections are made higher in the cord, there is a larger margin of safety.

From the results obtained in this series of patients, it is obvious that the injection of alcohol into the subarachnoid space is not a panacea for the severe pain produced by extensive genital carcinoma. The fact that over half of the motor and sphincter disturbances occurred in the 8 patients obtaining good relief is significant. Apparently these patients obtained relief because sufficient alcohol was injected to give a high spinal fluid concentration over a relatively wide area. This caused extensive destruction of both the anterior and posterior roots and probably changes in the cord itself that were clinically comparable to those seen in partial transverse myelitis.

When considering the possible deleterious effects of subarachnoid alcohol injection as a therapeutic measure for intractable pain, there are several mitigating factors. Most of the gynecologic patients who receive such treatment are in the late stages of carcinoma and have a very limited life expectancy. Some are already con-

fined to bed and the others soon will be. Therapy necessarily revolves around the relief of pain, which often is extremely severe. The alternatives are presacral sympathectomy, dorsal root resection or increasing doses of opiates, any of which may be objectionable. Since the injection of alcohol is a simple and often effective procedure, it is felt that in many cases the chance for relief outweighs the possibility of untoward effects.

#### SUMMARY AND CONCLUSIONS

Twenty-two patients with incurable and advanced genital carcinoma associated with severe pain were treated with subarachnoid injections of alcohol. It was found that:

1. When the pain distribution indicates involvement below the eleventh thoracic cord segment, the injection of strong alcohol into the subarachnoid space may occasionally give excellent relief, but more frequently the relief is incomplete or of short duration.
2. Such injections are often followed by serious permanent motor and sphincter disturbances.
3. There is an apparent correlation between the degree of relief obtained and the amount of the resulting motor and sphincter disturbance.

#### RESULTS OF INJECTIONS

All injections were made below the 11th thoracic vertebra. Unless otherwise specified:

"Transitory" refers to a period of seven days or less.

"Relief" refers to a period of more than seven days.

1. H-13254. Pain in lower abdomen, right hip, and leg. 1.75 c.c. of absolute alcohol. Urinary incontinence for 10 days, lower abdominal pain decreased, leg and hip pain persisted. No relief.
2. K-5223. Severe lower abdominal pain. Quantity of alcohol not stated. Immediate transitory numbness in left leg. No relief.
3. 38-16536. Deep pelvic and right groin pain. 1.5 c.c. of alcohol, repeated following day with patient lying on opposite side. Amelioration of pain for 3 days. Recurrence with full intensity. Permanent urinary incontinence and mild bilateral paresis.
4. H-93. Low abdominal pain more pronounced on right. 1.0 c.c. of 95 per cent alcohol with transitory numbness of the right lower extremity. No relief.
5. K-6773. Low abdominal, right hip and leg pain. 1.5 c.c. of absolute alcohol. Slight transitory improvement complicated by persistent motor paralysis.
6. K-8116. Low abdominal and bilateral leg pain. 0.75 c.c. of absolute alcohol, repeated following day with patient lying on opposite side. Transitory numbness and burning in legs. Numbness persisted. No relief from pain.
7. 38-22200. Right flank and leg pain which disappeared immediately following 0.9 c.c. of absolute alcohol but recurred in 2 days.
8. 39-9129. Deep pelvic, left groin, and leg pain. 0.7 c.c. of absolute alcohol, repeated following day with patient lying on opposite side. Transitory urinary incontinence and diminution of pain in left leg. Recurrence in 3 days.
9. 38-41459. Deep pelvic and right leg pain. 0.7 c.c. of absolute alcohol. Patient thinks she obtained very slight transitory improvement.
10. M-13116. Low abdominal and left leg pain. 1.5 c.c. of 95 per cent alcohol resulted in persistent difficulty initiating urination. Partial relief.
11. 38-28705. Deep pelvic and right leg pain. 1.0 c.c. of absolute alcohol gave transitory burning and numbness. There was an incomplete paralysis of right leg which slowly decreased after 10 days. Partial relief.
12. K-3036. Deep pelvic pain. 0.6 c.c. of absolute alcohol. Transitory numbness and motor paralysis of left leg lasting 36 hours. Slight relief.
13. P-6217. Severe lumbosacral pain. 1.0 c.c. of absolute alcohol. Permanent urinary incontinence and slight relief.

14. P-8322. Deep pelvic pain. 0.75 c.c. of absolute alcohol resulted in transitory numbness with partial relief.

15. J-3773. Pain in left hip and leg. 0.75 c.c. of absolute alcohol. Immediate and complete relief.

16. K-8192. Pain in lower abdomen and right leg. 1.5 c.c. of absolute alcohol with immediate relief lasting for 6 months.

17. 39-12607. Pain in pelvis and left leg. 0.9 c.c. of absolute alcohol resulted in transitory burning and numbness. There was partial paralysis of right leg. Good relief during 30-day observation period.

18. K-9944. Deep pelvic pain. 0.6 c.c. of alcohol with immediate partial relief lasting 21 days.

19. 38-41607. Low abdominal and bilateral leg pain. 1.0 c.c. of 95 per cent alcohol, repeated following day with patient on opposite side. There was persistent bilateral incomplete motor paralysis and relief lasting 14 days.

20. 39-3812. Deep pelvic and right leg pain. 1.0 c.c. of 95 per cent alcohol. Persistent urinary incontinence and right motor paresis. Complete relief lasting 60 days.

21. 39-2564. Abdominal and right hip pain. 0.7 c.c. and 0.8 c.c. of absolute alcohol on left and right on successive days. Persistent urinary incontinence and bilateral paresis. Complete relief from pain.

22. 39-869. Pain in right leg. 1.0 c.c. of absolute alcohol. Transitory burning, numbness, and urinary incontinence. Paralysis of right leg but relief from pain during observation period of 7 days.

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## FIBROMA OF THE OVARY WITH ASCITES AND HYDROTHORAX

### A CLINICAL AND PATHOLOGIC STUDY WITH REPORT OF TWO CASES

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**S**OLID fibromatous tumors of the ovary are no longer considered rare nor of particular clinical significance. However, their occurrence associated with ascites and hydrothorax (frequently referred to as Meigs' syndrome) presents an extremely interesting clinical and pathologic entity, both as a diagnostic problem and as a condition which, in spite of a clinical picture of grave appearance, is almost magically relieved by surgery. Its recognition, therefore, is important to both clinicians and pathologists. This condition exemplifies an apparently benign tumor capable of producing effusions into two of the major body cavities (abdominal and pleural) without any detectable local or remote anatomic changes. Although this tumor is histologically benign, it produces a picture clinically simulating a pelvic malignancy with peritoneal and pulmonary or pleural metastases.

We are here reporting two such cases. One is fairly typical. The other is somewhat atypical, but illustrates the fact that a fatal termination may result if surgical treatment is too long delayed.

Although Meigs and Cass, in 1931, called attention to solid fibroma of the ovary associated with ascites and hydrothorax as a clinical entity, other authors previously had noted these changes. Mapes<sup>2</sup> in 1909 noted ascites as a concomitant symptom of solid fibroma of the ovary, but did not mention hydrothorax. In 1913 Titus<sup>3</sup> emphasized the presence of ascites in one-half of the cases of fibroma, and although his patient had chest findings, no mention of hydrothorax was made. The symptoms referable to the heart, i.e., dyspnea and orthopnea, he ascribed to the size of the tumors or to the ascites. In 1923, both Owen<sup>4</sup> and Hoon<sup>5</sup> independently described the presence of hydrothorax which disappeared following the surgical removal of the ovarian fibroma. Ascites was also noted by both authors.

CASE 1.—Mrs. G. M., a 45-year-old, white housewife, had been aware of the presence of a mass in her lower abdomen for about one year, during which time it had gradually increased in size. For about a year previous to the occurrence of her menopause she had noticed a prolongation of her menses and the passage of numerous blood clots in the flow. Following the menopause, however, there had been no further vaginal bleeding of any kind.

She stated that she was annoyed by a constant bearing-down sensation in her lower abdomen. She had also been troubled by a sacral backache for some time. During the two months preceding her admission to the hospital, she had lost twelve pounds in weight in spite of a fairly good appetite. At times she experienced edema of the feet and ankles, heart-consciousness, palpitation, slight dyspnea, and left thoracic pain on deep respiration.

The patient had been told that she had "thyroid and heart trouble." Her menopause had occurred one year previously, and there had been no postmenopausal bleeding.

*Physical Examination.*—The patient was a fairly well-nourished, well-developed, white female in no immediate distress. Her temperature, pulse, and respirations were normal. Her blood pressure was 120/70. The thyroid gland was not palpable. There was dullness in the lower chest bilaterally with some diminution in intensity of breath sounds on the left side. The left heart border was displaced laterally, and there was a soft systolic murmur at the apex. In the lower abdomen just above the symphysis pubis, a nontender baseball size, hard, smooth mass could be palpated. Vaginal examination revealed only the presence of the mass felt abdominally but yielded no additional information as to its origin or nature.

*Laboratory Findings.*—The blood and urine were essentially normal. The basal metabolic rate was -10 per cent. Electrocardiographs were reported as showing "evidence of extensive myocardial damage on a probable arteriosclerotic basis." Chest x-rays yielded the following: "There is a dense homogeneous shadow occupying the left base with its upper border definite and oblique and parallel to the anterior fifth rib. This shadow obliterates the diaphragm and costophrenic angle." Re-examination one week later confirmed these findings.

*Preoperative Diagnosis.*—On the basis of the above findings and a surgical consultation, a diagnosis was made of papillary adenoma of the ovary, probably malignant, with organic heart disease and left pleural effusion. Exploratory operation was advised.

*Operation.*—Operation was performed on Nov. 22, 1937, three weeks after admission to the hospital. There was free serous fluid in the peritoneal cavity. A large solid tumor of the left ovary was found. There were also several small uterine fibroids and a cystic mass in the left broad ligament. The right ovary was slightly enlarged and sclerotic. No enlarged lymph nodes nor any gross evidence of malignancy was seen. The left ovarian tumor and the cyst in the left broad ligament were removed.

The postoperative course was entirely uneventful and the patient was discharged on Dec. 4, 1937, the thirteenth day after operation, in good condition and much improved. When last seen in April, 1939, approximately sixteen months later, she was entirely well and had no complaints.

*Pathologic Examination.*—The specimen consisted of an ovary converted into a firm solid mass measuring 17 by 13 by 5 cm. The surface was smooth, purple-



gray to yellowish tan, and in the capsule there was a single dilated and congested blood vessel. On sectioning, the cut surface was homogeneous light grayish tan and trabeculated. Microscopic examination showed the tumor to be composed of interlacing bundles of cellular fibrillar tissue. The nuclei were large, oval-shaped, and regular. There were no evidences of malignancy. The pathologic diagnosis made was benign cellular fibroma of the ovary.

CASE 2.—Mrs. R. S., 37 years old, colored, was admitted to the hospital on Sept. 11, 1930, complaining of pain in the right upper quadrant of her abdomen of three weeks' duration. The pain was sharp and constant, radiating to both sides of the back and had become more severe on the day of admission. On that day she had developed pains in the lower abdomen, recurrently cramplike in character, and resembling labor pains. She had been attending a prenatal clinic for some time and had been told that if the pains became more severe it would be necessary for her to enter the hospital. She stated that she had been aware of a palpable mass in her lower abdomen for at least four months.

The medical and surgical history were irrelevant. Her menses had been normal until the onset of her pregnancy. Her obstetric history included 9 pregnancies and 7 normal deliveries. She had two miscarriages and one of her babies had been a breech presentation delivered by "instruments."

*Physical Examination.*—The patient was poorly nourished and appeared to be in severe pain. Her temperature was 98° F.; pulse, 128; respirations, 24; and blood pressure 154/120. There was a nodular enlargement of the thyroid gland. The breasts were enlarged and colostrum could be expressed from both. The abdomen was distended asymmetrically with a large bulging mass on the right side which was hard and tense, and a smaller softer mass on the left side, the two together extending to the level of the xyphoid. Fetal heart tones could not be heard. On vaginal examination the cervix was found to be soft, the external os closed. There was a pitting edema of both lower extremities.

There were no significant laboratory findings.

On the basis of the above data a diagnosis of pregnancy with fibroids and eclamptogenic toxemia was made. However, the possibility of malignancy of the ovary complicating pregnancy was strongly considered.

Three days after admission, the patient delivered a dead six months' fetus, followed by spontaneous expulsion of the placenta. Examination showed a large hard rounded mass in the abdomen separate from the uterus. The patient's condition failed to improve and on Sept. 16, 1930, three days later, an exploratory laparotomy was performed under local anesthesia, and a large solid tumor of the left ovary with an unrecorded amount of free fluid was found. Because of the patient's poor condition, the mass was not removed. However, a biopsy was taken from it. Her condition remained poor following operation and on September 18, two days later, she died.

*Autopsy.*—(Performed by R. H. Jaffé.) Autopsy was performed on the day of death and the pertinent findings consisted of the following: There was a huge spherical firm tumor mass of purple gray color occupying the midportion of the abdominal cavity, displacing the liver, stomach, and transverse colon upward and the small intestines to the left and downward. This mass measured 29 cm. in transverse diameter, 27 cm. in vertical diameter, and 16 cm. in anteroposterior diameter. It weighed 7,150 Gm. The surface of the tumor was cloudy and covered by thin fibrinous tags. Its origin was the left ovary and its pedicle was formed by the Fallopian tube, ovarian ligament, and mesosalpinx, and was twisted through 330 degrees. There were dilated lymphatics in the mesovarium, and the veins were filled with light purplish red thrombi. On section, the cut surface was light, purple gray to dark purple and very firm, although it contained several up to 10 mm. cavities with a smooth lining and filled by a clear watery fluid. There was about 150 c.c. of cloudy, reddish brown fluid in the pelvis. The left pleural cavity contained about 700 c.c. of brownish fluid and the right about 50 c.c.

Microscopically, the tumor was composed of slender, spindle-shaped cells between which there were, at regular intervals, bundles of collagenous fibrils. The

nuclei of these cells were long and flat, with pointed buds, and were rich in chromatin and quite regular in size and shape. Between these bundles there was a moderate number of dilated blood vessels. There were many areas of diffuse necrosis and hemorrhage. The necrotic and living tissues were separated by a narrow zone of edematous tissue. The tumor possessed an edematous capsule which was less cellular than the tumor and showed wide thrombosed blood vessels.

*Anatomic Diagnosis.*—Twisted large fibroma of the left ovary with hemorrhagic infarction and necrosis, acute glomerulonephritis, bilateral hydrothorax, ascites, and nodose goiter.

#### COMMENT

Case 1 is fairly typical of this syndrome in all its aspects and demonstrates the various factors brought out by Meigs<sup>6</sup> and Meigs and Cass.<sup>1</sup> The patient had been hospitalized because of symptoms suggestive of cardiac failure. However, after the abdominal mass was discovered and x-rays revealed a hydrothorax, a diagnosis of malignancy of the ovary was made. This illustrates the value of emphasizing the importance of this syndrome. If the case had come to rest at this point on the conclusion that the patient was suffering from a hopeless condition of malignancy with metastases, the outcome would have been somewhat different from the satisfactory result finally attained. Operation had disclosed the actual cause of her symptoms.

Case 2 presents another aspect of the situation. Although the patient had a large ovarian fibroma, bilateral hydrothorax, and ascites, the picture was complicated by a pregnancy terminating at six months in eclamptogenic toxemia and spontaneous abortion. Death of the patient occurred two days after an exploratory operation in which the ovarian tumor and ascites were discovered.

In analyzing the events leading to her death, three possible mechanisms are to be considered. First, did the presence of a large ovarian tumor interfering with the progress of gestation and producing abortion, combined with the effects of toxemia and an exploratory laparotomy, cause her death? Second, did she die from the acute glomerulonephritis which was observed on microscopic examination? Third, one may consider as a cause of death an untreated Meigs' syndrome. That death may occur in this disease is brought out by Meigs<sup>6</sup> who reports a case in which the patient died without operation.

Meigs' syndrome may be defined as a clinical entity in which a benign fibroma of the ovary is accompanied by a serous transudate in the peritoneal cavity and in one or both pleural cavities.

The condition may occur at any age after maturity, but is most often discovered in the early postmenopausal period. However, cases have been reported as occurring in patients 36 and 64 years of age.<sup>1, 7</sup> The true frequency of occurrence is difficult to determine, since these cases are usually included in the group of ovarian fibromas in general. The incidence of ovarian fibroma is reported by various authors as ranging between 2 per cent and 4 per cent<sup>5, 8</sup> of all ovarian tumors. Among our cases (autopsy and surgical material) fibromas make up 7.6 per cent of all ovarian tumors or 9.9 per cent of the benign group. According to Meigs and Cass,<sup>1</sup> in their review of the literature, they found that various authors report 13.7 per cent to 40 per cent of ovarian fibromas are accompanied by ascites.

Clinically in both of our cases there were features which suggested cardiac weakness with resulting circulatory disturbances. In Case 1 this is substantiated by the electrocardiographic findings. It is possible that in a patient who has a subclinical or compensated cardiac weakness in which the cardiac reserve is just sufficient to withstand the strain of the patient's activities, the added stress thrown on the heart by the pressure of the heavy ovarian fibroma, combined with its possible interference with pelvic and lower abdominal circulation, may be sufficient to produce a low grade cardiac decompensation, resulting in ascites and pleural effusion. This explanation is supported by the necropsy findings in one of the cases.

## SUMMARY

Two cases of benign solid fibroma of the ovary associated with ascites and hydrothorax are here described.

In both patients the left ovary was the site of the tumor, and the patients' ages were 45 and 37 years, respectively.

The hydrothorax was on the left side in one case and bilateral in the other.

A mild cardiac decompensation is suggested as the cause of the ascites and hydrothorax, as disclosed by the necropsy in the second case.

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## GRANULOSA CELL TUMOR OF THE OVARY WITH HEMOPERITONEUM AND HEMOTHORAX\*

## REPORT OF A CASE

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WITH the growing interest in granulosa cell tumors of the ovary, I wish to add this very interesting case to the literature. The presence of hemoperitoneum and hemothorax in association with any abdominal tumor must certainly carry a suspicion of a metastatic neoplastic process until definitely ruled out. In this case there was a rapid postoperative recrudescence to a normal physiologic and anatomic state, and the patient is symptom free after two years. This relatively short period of observation is not sufficient to comment on the relatively low degree of malignancy of granulosa cell tumors in general with any degree of confidence.

The patient, well developed, obese, 44 years old, first complained of a dull aching pain in both lower quadrants of the abdomen, more severe on the right, of two and one-half months' duration. The onset immediately followed a seven-day attack of dysentery. There had been constant nausea and anorexia and periodic vomiting for nine weeks. The patient had noted an increase in the size of the abdomen of one week's duration.

The patient had always been well. She was treated for sterility eighteen years previously, at which time a dilatation and curettage had been performed and a stem and Smith pessary was used for six months. Ten years ago the patient had an abdominal hysterectomy because of fibromyomas.

The menses had always been regular, every twenty-eight days, lasting three days, since the menarche at the age of fifteen until the removal of the uterus ten years ago. There have been no menopausal symptoms, remote or recent.

Upon admission the positive physical findings were: A tensely distended abdomen, but no tenderness and no masses palpable. A fluid wave was present. Pelvic examination revealed a normal cervix but the cul-de-sac and fornices were bulging, due to increased intra-abdominal pressure. No mass could be demonstrated. The lung fields were clear. The admission urine specimen was normal. The leucocyte count was 7,150, the erythrocyte count 4.22 million, and the hemoglobin 61 per cent (Sahli).

\*With the permission of W. H. Weir and A. J. Beams.

The patient was subjected to complete roentgenologic investigation. The colon, gall bladder, esophagus, stomach, and duodenum were reported normal. The small intestinal series revealed all the small intestines situated in the right upper quadrant of the abdomen and in the epigastrium (see Fig. 1). The loops emptied readily. Roentgenograms of the chest revealed the diaphragm elevated bilaterally, but both lung fields were clear.

During the eight-day period of hospitalization, the patient remained distended but without pain. There was constant nausea. She was discharged upon her request on the eighth day.

The patient was re-admitted one week later. During this time the abdomen had increased in size, and she had developed extreme shortness of breath and a dry cough. Examination revealed the expansion of the thorax markedly restricted, especially on the left. Vocal fremitus and breath sounds were absent and the percus-



Fig. 1.

sion note was flat. The right lung field was clear. The heart was displaced to the left (Fig. 2). There was pitting edema of the lower legs. No change in the abdominal signs were noted except that a small ecchymotic area was observed surrounding the umbilicus (Cullen's sign). The urine was normal, the blood count showed an increasing anemia, the sedimentation rate was rapid, and the blood chemistry was normal.

Thoracentesis and paracentesis revealed grossly bloody fluid. Inasmuch as the presumptive diagnosis (pelvic tumor) was open to doubt, exploratory laparotomy was deemed advisable.

The patient was induced and maintained with evipal intravenous anesthesia because of the respiratory embarrassment. A large aspirating needle was introduced into the left thorax and approximately 500 c.c. of bloody fluid was first removed. A small suprapubic incision was then made. Upon opening the peritoneum, there was a gush of serosanguinous fluid. Palpation revealed the presence of a mass arising

from the pelvis. The incision was enlarged and an encapsulated, gray colored "meaty" tumor, approximately 25 cm. in diameter was found involving the left ovary. It was adherent in the cul-de-sac and to the posterior sheath of the left broad ligament. In attempting to free up the mass, the capsule was ruptured, and it was then removed piecemeal. The abdomen was washed with 8 liters of normal saline solution.

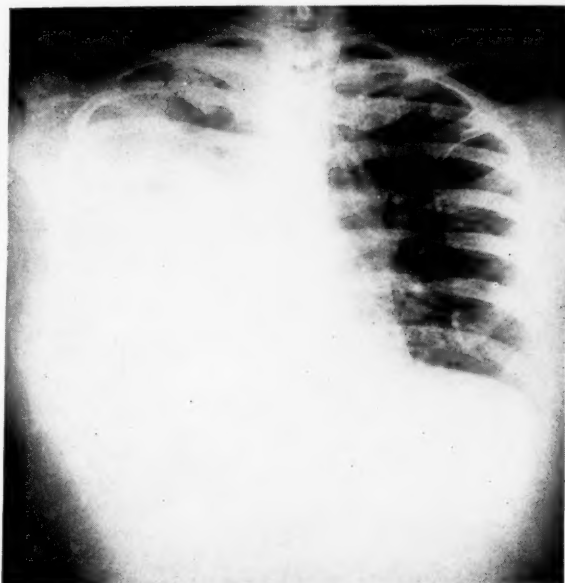


Fig. 2.

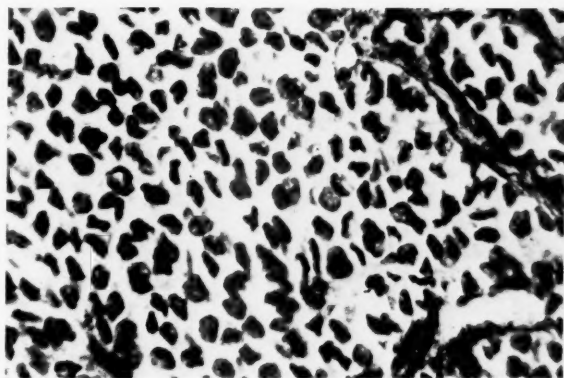


Fig. 3.

The postoperative course was uncomplicated. Physical signs referable to the left chest gradually disappeared and the abdominal ascites did not recur. Upon discharge from the hospital on the fifteenth postoperative day, there was good expansion of the lung and excursion of the thorax, and there was no evidence of remaining fluid.

The patient has been examined regularly since her discharge from the hospital and has been subjected to repeated fluoroscopic and roentgenologic examinations. There has been no evidence of recurrence by pelvic examination.



*Pathologic Report 1.*—The specimen consisted of a cyst wall 28 cm. in diameter. The surface was smooth, gray pink, and glistening. The inner surface was covered by a rather thick layer of yellow-pink, somewhat granular tissue several centimeters thick. It had a tendency to be piled up in an irregular papillary manner. There was considerable fibrous tissue in the tumor mass.

Histologic examination of the tissue revealed a very cellular tumor growing in broad compact groups of cells. The individual cells were uniformly small and round or ovoid in shape, although in some areas they were elongated and of spindle type. The nuclei were vesicular and the cytoplasm abundant but poorly defined. Thin bands of connective tissue separated the masses of cells into poorly defined alveoli. There were a moderate number of mitotic figures. The tumor showed no differentiation. There was suggestive papilliferous arrangement in a few areas. There was no involvement of the capsule although small groups of cells were present just within the outer band of connective tissue of it. The type of neoplastic cell definitely resembled a granulosa type. *Diagnosis:* Malignant granulosa cell tumor (Fig. 3).

*Pathologic Report 2.*—The pleomorphism of the cells was not uncommon in granulosa cell tumors. There was no invasion of the capsule. The presence of a tiny amount of fat in the essential cells, together with their loose cytoplasm indicated a small amount of luteinization. The cellular parts of the tumor were devoid of reticulum; the lesion was therefore not a thecoma. The supporting tissue showed a rich reticulum which, in a few places, suggested the arrangement of theca interna. There was not adequate reason for considering this tumor as malignant. *Revised Diagnosis:* Granulosa cell tumor of the ovary with slight luteinization.

The lack of concurrence of opinion in the histopathologic examination of the tissue of this tumor is significant. It is obvious the variation in the two interpretations described above regarding the question of malignancy permits no compromise. It seems, therefore, that the criteria for malignancy in all granulosa cell tumors is not clearly defined; that there are instances in which these are subject to the element of individual interpretation, which may be variable. I quote Dr. Howard T. Karsner:\* "There are several difficulties in the microscopic diagnosis of malignant granulosa cell tumors. With ordinary fixation it may be difficult to distinguish between true epithelium such as occurs in carcinoma, and granulosa cells. The matter of the diagnosis of malignancy is thus confused by the frequent lack of distinction between granulosa cells and epithelial cells. . . . The trabeculae of the (benign) granulosa cell tumor suggests an invasive growth, but they show a gradual merging with the enveloping capsule in contrast to the customary sharp distinction of invading carcinoma. The malignant granulosa cell tumor grows into and through the ovarian capsule and sections often show nodular masses associated with widespread hemorrhage and necrosis."

The frequency of mitoses is apparently not significant.

Hemoperitoneum and hemothorax, in the absence of known primary etiologic factors and in association with a "malignant" tumor, are usually presumptive evidence of a metastatic invasion of the peritoneum and pleura. In the absence of a proved metastatic involvement of these structures we are unable to explain the presence of the serosanguineous collection of fluid. It is well known however, that solid tumors of the ovary are often associated with abdominal ascites and even hydrothorax, yet the mechanism of the formation of these fluids has not been satisfactorily explained. In view of the rapid recovery of our patient I believe it is safe to dismiss the possibility of peritoneal or pleural carcinomatosis. It has, on the other hand, been observed that with the removal of the ovarian influence there is a temporary arrest, even regression, of the activity of metastatic as well as primary lesions.

Qualitative examination of the chest fluid for the presence of estrogenic substances might have revealed information valuable not only in the explanation of its etiology, but possibly in the further understanding of these tumors. Assuming a positive estrogenic titer to be present, ectopic secreting foci within the pleura are conceivable; their disappearance, or the disappearance in their activity, possibly following the removal of the ovarian influence.

\*Certain Ovarian Tumors Associated with Sexual Endocrine Dysfunction, *Transactions and Studies, College of Physicians of Philadelphia* 1: 301, 1940.

## SUMMARY

A case of granulosa cell tumor of the ovary associated with hemoperitoneum and hemothorax is reported. Although this case initially simulated a true malignancy, there has been no evidence during the past two years of observation which would substantiate this impression.

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10515 CARNEGIE AVENUE

## CARCINOSARCOMA OF THE UTERUS

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EWING<sup>1</sup> collected 10 cases of carcinosarcoma of the uterus up to 1928 and in the same year Newell<sup>2</sup> found 20 cases reported. Since 1927 three cases have been reported in the English literature,<sup>2-4</sup> one in French by Daniel and Lazaresco<sup>5</sup> and one in German by Breiter.<sup>6</sup>

Saphir and Vass,<sup>7</sup> in their review of the reported cases of carcinosarcoma, are not convinced that all of them are actually carcinoma and sarcoma. Of the 153 cases which they reviewed only three or four qualified as multiple neoplastic processes. Of 36 cases occurring in the uterus, they did not believe any to be true coexisting carcinoma and sarcoma. The most common sources of error in interpretation were based upon the suggestive appearance of sarcoma because of a marked stromal reaction to the invasion of carcinoma, the extreme variability of epithelial cells, especially when transitional or spindle forms were present, and the part which chronic inflammation may play in the production of pleomorphic cells resembling sarcoma. Therefore, these authors question the coexistence of carcinoma and sarcoma in the great majority of the reported cases.

## CASE REPORT

Mrs. W. T. A., a white widow, 62 years of age, was admitted to the Emory University Hospital on July 16, 1939, complaining of an abdominal tumor, leucorrhea, and some vaginal "spotting" for the past two years. During the preceding eight years a slowly growing tumor mass had been noted in the lower abdomen, but there had been no discomfort until July 5, when she had a sudden severe pain in the left lower quadrant sufficient to cause her to go to bed and call a physician. Ice packs to the abdomen and the use of sedatives were followed by complete relief of the pain in twenty-four hours, with no recurrence after this attack. Her physician then advised hospitalization for the removal of her tumor.

*Past History.*—Menopause occurred thirteen years ago. No operative procedures had ever been performed, and she had always been in good health except for occasional shortness of breath during the past two years.

*Physical Examination.*—The patient was a well-developed and slightly obese white female in no apparent distress. Her temperature, pulse, and respiration were normal. The blood pressure was 170/110, and there was some cardiac enlargement of the left ventricular type. On abdominal palpation a large, firm, fixed tender mass was found almost filling the pelvis. Vaginal examination revealed a normal cervix with the uterus pushed to the left and enlarged apparently from the pressure of

fibroids and was only slightly movable. A large rather firm and well-fixed mass filled the right lower quadrant. The inguinal lymph nodes appeared to be normal. The clinical impression was malignant ovarian tumor, fibroid tumors of the uterus, and hypertensive heart disease with early congestive failure.

Roentgenogram of the chest revealed the lung fields to be clear except for some congestion in both lower lobes. Also the cardiac shadow indicated a slight left ventricular enlargement. The patient was given digitalis for the congestive failure and the uterus, tubes, and ovaries were removed.

*Tissue Examination.*—The uterus measured 12 by 8 by 7 cm. The increase in size was caused mainly by a soft, well-circumscribed mass located in the fundus of the uterus. It measured 6 cm. in diameter and grossly resembled a fibromyoma with degenerative changes. On cross section, this mass was found to be composed of soft, moist, glistening white tissue in which there were numerous small irregular

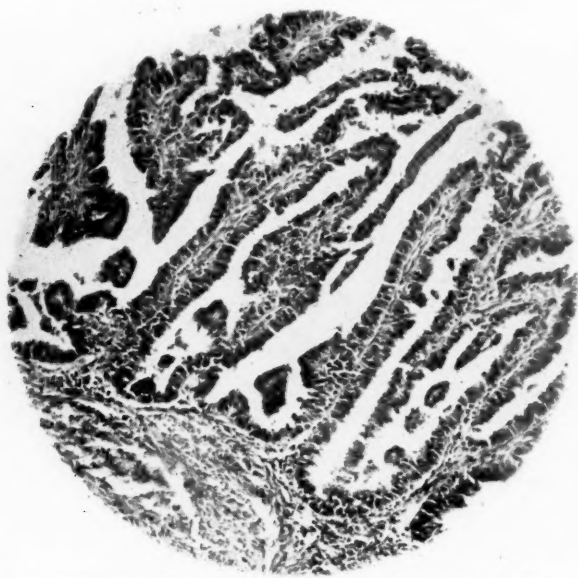


Fig. 1.—Papillary carcinoma of the endometrium.

areas that were filled with clear light yellow fluid, giving the impression of edematous degeneration or sarcomatous change of a uterine fibromyoma. Several mural fibroid tumors without any degenerative changes were present in the other portions of the myometrium with the largest of these measuring 2 cm. in diameter. The endometrium just over the degenerated fibromyoma was soft, somewhat irregular, and measured 5 to 7 mm. in thickness. It grossly resembled a marked localized hyperplasia. The left ovary measured 2 by 2 by 1½ cm. and consisted largely of an atrophic fibrous mass. The right ovary was enlarged because of a cyst which measured 8 cm. in diameter and contained a chocolate brown serous material. On the inner surface of this cyst there were several soft light yellow elevated areas which were about 1 cm. in diameter and 6 to 7 mm. in thickness.

Microscopic sections of the endometrium show an unrestrained growth of epithelial cells, having a distinct papillary formation with numerous proliferating stalks and buds (Fig. 1). Very few solid areas of these active epithelial cells are present. Under high power these cells are round to polyhedral and columnar in shape, vary somewhat in size, with large hyperchromatic nuclei, and have a moderate amount of clear cytoplasm. Mitoses are fairly numerous and very

little inflammatory reaction is present. Several small areas of endometrial glands, typical of adenomyoma of the myometrium, are present in this section. This same microscopic picture of disorderly epithelial hyperplasia in papillary formation prevails in the sections of the ovary taken from the soft yellow elevated areas of the cyst wall (Fig. 2). Very little actual glandular formation is seen in either of the tumor areas, being almost entirely papillary in type. The question arises whether these endometrial and ovarian tumors are separate papillary carcinomas, or whether it is a primary tumor in the uterus with ovarian metastasis, or possibly primary in the ovary with metastasis to the uterus. It is most likely that the carcinoma began in the endometrium and metastasized to the ovary. This is concluded from the appearance of such sections as seen in Fig. 1, which shows a small area of normal endometrium and when the lymphatic drainage of the uterus and ovary is considered. The lymphatic collecting channels of the uterus have their principal drainage from four or five vessels of the

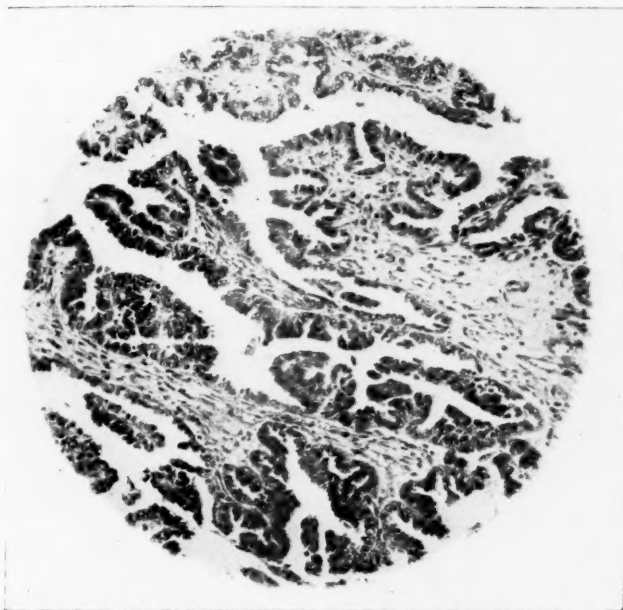


Fig. 2.—Papillary carcinoma of the ovary.

fundus which pass laterally through the broad and suspensory ligaments of the ovary and follow the ovarian vessels to the lumbar and pre-aortic nodes. There are others which pass laterally with the uterine vessels to the iliac nodes, and some smaller ones that follow the round ligament to terminate in the inguinal nodes. The lymphatics of the ovary follow the ovarian blood vessels to end in the lumbar nodes. Thus the chance of metastasis of a primary tumor of the ovary to the uterus is quite unlikely and even though this did happen through aberrant lymphatic channels or retrograde extension, the ovarian metastasis should occur on the serous surface of the uterus rather than in the endometrium.

Microscopic sections of the large mural fibroid consist in part of masses of small deeply stained undifferentiated cells (Fig. 3) which under high power are seen to be round or polyhedral in shape with very little cytoplasm. A moderate number of mitoses are present and such areas are interpreted as being true myosarcoma. In other areas of this same section there is a considerable amount of glistening hyaline tissue in which are numerous islands of well-preserved hyper-

chromatic fibroblasts or myoblasts that are grouped around the smaller vessels. At no place can there be seen the usual whorls of smooth muscle tissue and bundle formation usually seen in fibroids.

Postoperative radiation to the pelvis was carried out in the Winship Clinic of Emory University Hospital. Fifteen hundred roentgen units were given anteriorly over each lower abdominal quadrant and a like number posteriorly over each gluteal region at the level of the sacrum and lower lumbar vertebrae. The dosage was divided into 300 r. each day, by alternating successively at the four areas, with 200 kilowatts through a composite filter at a distance of 50 cm., and through a port 20 by 10 cm. At this time, three months after operation, no further metastasis has been found.

In the case presented, the myosarcoma and the papillary carcinoma of the uterus are believed to be two separate entities, that is, multiple primary malignant tumors, each having its own histologic characteristics. Since the predominant feature of this carcinoma is its papillary arrangement without any surrounding fibrosis, there is little reason to interpret the separate sarcoma as an extreme fibroblastic reaction to the carcinoma. Likewise there is no inflammatory change present which might serve as the cause for an extreme fibroblastic reaction.

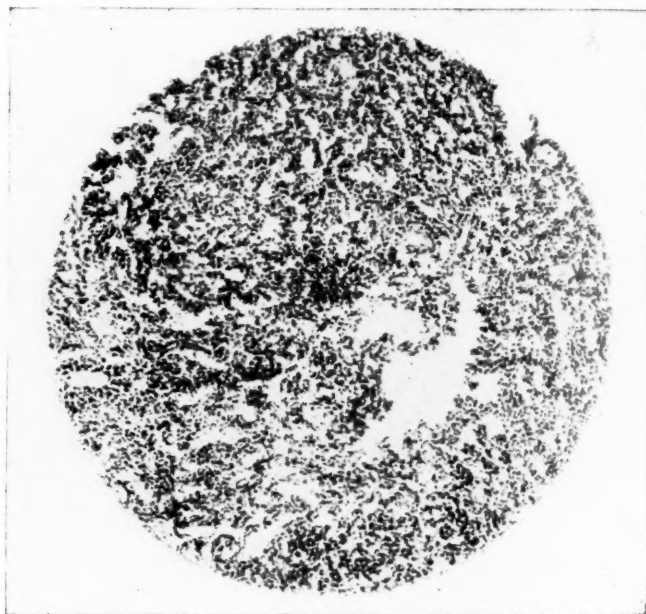


Fig. 3.—Small cell (myo-?) sarcoma in fibromyoma directly under the tumor of the endometrium.

The occurrence of myosarcoma of the myometrium and an overlying papillary carcinoma of the endometrium with ovarian metastasis is especially interesting from the viewpoint of the possible influence the myosarcoma or the fibromyoma might have had on the development of the adjacent endometrial carcinoma. This has been discussed by Ewing<sup>1</sup> as well as others.

#### SUMMARY

A case is reported in which there was a papillary carcinoma of uterine endometrium with metastasis to one ovary and a sarcoma in the adjacent fibromyoma.



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RIGHT UTERUS UNICORNIS ASSOCIATED WITH  
RENAL AGENESIS

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TRUE uterus unicornis is a very uncommon abnormality and its association with renal agenesis is very rare. This anomaly must be differentiated from the so-called unicornuate uterus with a rudimentary horn. The latter condition is seen more often than the former and is also sometimes associated with unilateral renal agenesis. Schumacker<sup>1</sup> was able to find only 28 cases in the literature, of true unicornuate uterus. Since his review no cases have been reported.

It is during the sixth week of development that the Müllerian ducts are seen and they are located at the ventrolateral aspect of the Wolffian ridges. In approximately one week's time, each Müllerian duct contacts the cloaca and eventually a lumen develops. In the male, these ducts begin to atrophy in about the third month while in the female they continue to develop. The proximal portions of these ducts form the Fallopian tubes and the distal portions unite to form the uterus and vagina. The medial wall formed by the fusion of both Müllerian ducts degenerates and a single uterus and vagina are formed. Condensation of the mesenchyme within the inguinal folds of peritoneum gives rise to the round ligament.

It is by a deviation from the normal or arrestment at certain stages in development of the Müllerian ducts that various types of malformations of the uterus arise. Unilateral or bilateral failure of development may occur in the first month. A double uterus and vagina (uterus didelphys) may form during the second month because of the failure of fusion of both sides. There may be arrestment of development on one side giving rise to a rudimentary horn. Uterus bicornis may form during the third and fourth months because of incomplete fusion of the two Müllerian ducts or an arcuate uterus may develop. A persistence of the septum or a single or double cervix may develop. The only malformation that occurs after the fifth month is an arcuate uterus. It is also possible that a uterus may appear normal externally but there may be a persistent septum. This septum may or may not continue into the vagina giving rise to the uterus septus duplex or uterus and vagina septus duplex.

Schumacker<sup>1</sup> noted that the patient's ages varied from one day or less to seventy-six years. The anomaly was present in about 60 per cent of cases on the left side and in 9 cases the ovary and tube were completely absent on the defective side. In eleven other cases the ovary was ectopic and located above the pelvic brim. The ovary in general was usually longer and narrower on the

affected side. This was true of the findings in our case. When the Fallopian tube was present it was almost always a short portion of the fimbriated end. Usually the round ligament was present as a small, poorly developed structure attached to the cervical portion of the uterus. The broad ligament was absent on the defective side although occasionally a small remnant of it was present.

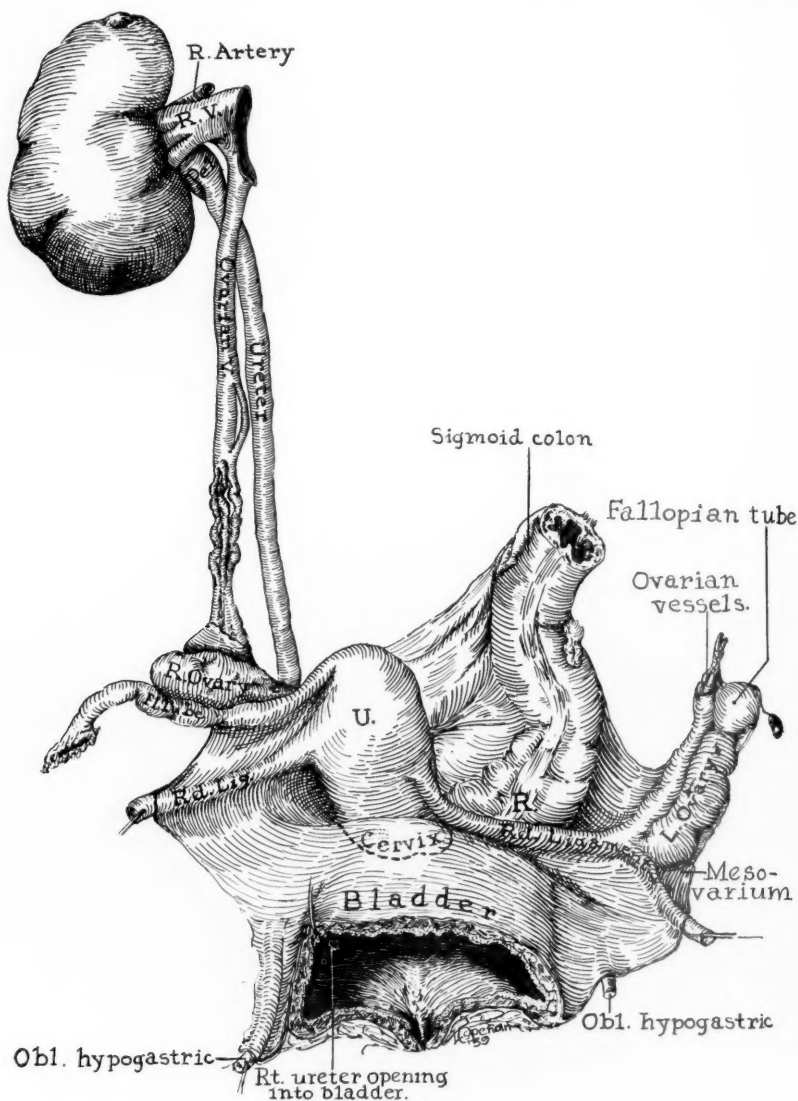


Fig. 1.—Diagrammatic representation of the uterine and renal anomaly and its relationships.

The ovarian ligament was found to extend down toward or into the internal inguinal ring. When the ovarian vessels were traced they were found to arise from the aorta or to enter the vena cava. The external genitalia were normal. The menstrual periods were normal or scanty, irregular, and painful. Cases have been noted in which multiple pregnancies occurred as well as abortions.

## REPORT OF CASE

M. R., a white married female, aged 32 years, was first admitted to the hospital on June 24, 1939, complaining of dyspnea and edema of the feet. Following her second and last pregnancy seven years ago, the patient noted occasionally edema of the eyes and face, most marked in the mornings. About one year before admission she developed dependent ankle edema and dyspnea which became progressively worse. She complained of occasional attacks of precordial pain and palpitation. During the last two weeks her appetite was poor. She had been married ten years and had two children, one seven and the other nine years of age.

Physical examination revealed a poorly developed and nourished, anemic, white female lying quietly in bed. The blood pressure was 254/148, temperature 99° F., pulse 90, and respirations 20. The tonsils were atrophic. A few crepitant rales were heard at both bases. The heart was questionably enlarged. P<sub>2</sub> was greatly accentuated and harsh. M<sub>2</sub> was split. No murmurs or friction rubs were heard. The liver was palpable to the level of the umbilicus. There was moderate pitting edema of the legs and ankles. The blood Wassermann was negative. The hemoglobin was 55 per cent, and the red blood cell count was 2,730,000. The urine was yellow and acid. The specific gravity was 1.005. Albumin was present and the sugar was negative. Microscopic examination revealed numerous epithelial cells and 3 to 8 pus cells per high power field. A Fishberg test revealed a variation of specific gravity from 1.007 to 1.010. Blood chemistry on June 26, 1939 showed a urea of 91 mg., creatinine of 6.66 mg., and a glucose of 95 mg. per 100 c.c. of blood. On June 29 a repeat blood chemistry showed a urea of 100 mg., a creatinine of 11.4 mg., and a sugar of 117 mg. per 100 c.c. A stool examination was positive for blood. An electrocardiogram showed definite evidence of myocardial disease. X-ray examination of the chest showed the cardiac shadow to be apparently enlarged and the borders were obscured by edema at the bases of the lungs. The patient was treated with transfusions, digitalis and a low protein and salt-free diet. She was discharged unimproved on June 29, 1939. The patient was readmitted on July 31 with an aggravation of previous symptoms. Her blood pressure was 170/110 and she was in marked respiratory distress. Moist rales were heard at both bases of the lungs up to the level of the eighth rib posteriorly. The heart was enlarged to the left and to the mid-axillary line in the sixth interspace. No murmurs were heard. The liver was enlarged 8 cm. below the costal margin, and there was evidence of fluid in the abdomen. The lower extremities showed moderate pitting edema extending up to the knees. Urine examination showed a specific gravity of 1.006, albumin was marked, sugar and acetone were negative, and the microscopic examination showed occasional white blood cells but no red blood cells. The blood urea was 120.4 mg., the creatinine 9.45 mg., and the glucose 136 mg. per 100 c.c. She was treated with concentrated glucose and other diuretics. Her condition became gradually worse. She developed a pericardial friction rub, went into coma and died on Aug. 15, 1939.

*Autopsy Report.*—The body was that of an underdeveloped and undernourished white adult female. The mouth showed poor oral hygiene. A decubitus ulcer measuring 2 cm. by 3 cm. was present over the sacrum. Moderate pitting edema of the feet, ankles and legs was noted. The main pathologic findings were intraperitoneal and intrapleural fluid accumulations. The lungs showed a few patches of bronchopneumonia. The heart was moderately enlarged and much fibrin was present on both pericardial surfaces. The spleen and liver were congested. The right kidney weighed 45 Gm. It was normal in position. The renal artery was patent but small in size. The capsule was thickened and adherent to the cortex. On stripping the capsule, the cortical surface was found to be roughly granular. At about its midportion, a large depressed scar was noted. The consistency was firm. The cut surface showed a markedly narrow cortex. The corticomedullary junction was indistinct. The medullary portion was narrowed. The pelvic mucosa was smooth and gray in color. The pelvis was dilated. The ureter was patent throughout. The urinary bladder was natural.

The left kidney and ureter were completely absent. There was no left ureteral opening in the urinary bladder. The uterus was a small unicornuate body, firm in consistency and measured  $6\frac{1}{2}$  cm. by 3 cm. by 2 cm. No definite point of demarcation was noted between the fundal and cervical portions. The uterus lay obliquely to the right in the pelvis with its upper end directed toward the right. The broad ligament on the right was small but intact. The uterine vessels were small in size. A well-developed round ligament ran from the fundus to the internal inguinal ring. The right tube arose from the cornual end and measured 8.5 cm. by 0.5 cm. A small subserosal cyst measuring 2 mm. in diameter was present in its midportion. The fimbriated extremity was open. The right ovary measured 3 by 1.5 by 0.7 cm. It appeared grossly normal and the ligaments were normal. On the left side there was no broad ligament or uterine vessels. The round ligament was thick and well developed. The left ovary was larger than the right and measured 4.5 by 1.8 by 0.7 cm. It lay vertically close to the internal abdominal ring. Its vessels entered at the upper end. From its caudal extremity a thin ovarian ligament extended toward the internal inguinal ring. At its upper border was a small cystic area measuring 1.5 cm. by 1 cm. Attached to it was a hydatid of Morgagni. This was the Fallopian tube, both ends of which were closed. Both ovarian veins entered directly into the inferior vena cava.

A case of true right unicornuate uterus associated with renal agenesis is reported, making the thirtieth case reported in the literature.

A short description of the embryology and the possible developmental anomalies likely to occur is noted.

The patient bore two children without difficulty but developed a chronic pyelonephritic contracted kidney and died in uremia.

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## CONGENITAL ATRESIA OF THE UPPER TWO-THIRDS OF THE VAGINA AND CERVICAL OS WITH HEMATOMETRA

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ACCORDING to the accepted embryologic authorities, the tubes, uterus, cervix, and vagina are constructed by the fusion of the Müllerian ducts and the hymen is formed by the union of the caudal ends of the Müllerian ducts and urogenital sinus. Some embryologists as Frazer<sup>1</sup> and Jordan<sup>2</sup> claim that the vagina has a dual origin, the upper two-thirds arising from the fusion of the Müllerian ducts and the lower one-third from a coalescence of the upper portion of the urogenital sinus and the lower ends of the Müllerian ducts. Dean Lewis<sup>3</sup> cites a case where there was complete absence of the tubes, uterus, cervix, and upper two-thirds of the vagina, while the lower one-third of the vagina and the external genitalia were present and normal, clinically proving the double origin of the vagina.

Robert Meyer<sup>4</sup> only recently wrote illuminatingly on the development and pathology of congenital closure of the vagina through a detailed study of a markedly atretic vagina in a girl fourteen days old who had come to autopsy. His former and present studies have revealed that the Müllerian ducts reached the urogenital sinus where they ended blindly; that the Müllerian ducts do not break through the urogenital sinus but instead, the sinus epithelium penetrates the

Müllerian ducts at the junction of the latter and the urogenital sinus; that the sinus epithelium displaces the Müllerian epithelium and matures to squamous epithelium; that if the vagina from the Müllerian ducts was first a tube, the tube becomes a solid cord filled by sinus epithelium whose inner cells undergo dissolution with a resultant re-formed tube. The substitution of the Müllerian epithelium by sinus epithelium arises at the meeting of both epithelia, Müllerian and sinus. If through a defect, the Müllerian ducts at the lower ends do not reach the sinus epithelium, the latter cannot penetrate into the Müllerian ducts. If one Müllerian duct shows such a defect, then only one-half of the vagina is penetrated by sinus epithelium. What occurs with the Müllerian epithelium of the closed side of the vagina depends upon the presence of a communication in the vaginal septum between the two halves of the vagina, and in such a case the normal sinus-vaginal epithelium would penetrate through the septum opening. If there is no septum communication between the two halves of the vagina there should be no possibility to substitute the Müllerian epithelium, then only would it show if the Müllerian epithelium itself is capable of building squamous epithelium. Meyer has shown, when there is persistent Müllerian epithelium, this epithelium will ripen into mucous membrane as it does in the cervix. This explains the presence of mucous epithelium, glands, cysts, and adenomas of the vagina on an embryologic basis. Autopsy specimens from the fourteen-day-old girl with atresia of the vagina showed both squamous and mucous epithelium. But atresias may originate not only because of faulty development but also after substitution of the Müllerian by sinus epithelium.

Atresia of the vagina may be congenital or acquired. Nagel and Veit, referred to by King,<sup>5</sup> believe that all types of atresias are acquired, because atresia of the vagina cannot be present with normally developed internal genitalia. They and King believe that before birth or early in life, as a result of gonorrhea, acute febrile diseases, irritating urine or irritating discharges associated with malnutrition and lowered resistance, ulceration and apposition of the vaginal walls may occur, with the resultant atresia of the same. Taussig in discussing King's paper rightfully denies that some form of vulvovaginitis is a prerequisite for atresia of the vagina. Clinically, Taussig's observations are the experiences of most of us, for gonorrheal and other nonspecific vaginitis is not infrequent in childhood, yet so few atresias subsequently develop or are found. He concludes that most prepubertal atresias are congenital and their presence is noted after puberty after symptoms arise.

Since congenital atresia of the vagina is possible, one should differentiate between such atresia and absence of the vagina. In the presence of an open hymen with a dimpling of about 2 cm. above the hymen with closure of the upper two-thirds of the vagina, shall we refer to such closure as atresia or absence of the vagina? Surely, to differentiate the two anatomic conditions one would have to section the rectovesical septum and examine histologically for the presence of fibromuscular tissue alone as it should occur in absence of the vagina or mixed with squamous or mucous epithelium or both as it should occur in atresia of the vagina. But such section of the rectovesical septum is not practical during an operation. However, clinically with a congenital atresia of the vagina one finds full development of the internal genitalia, and with absence of the vagina, there are other evidences of lack or malformation of the Müllerian ducts.

There are comparatively few cases reported in the literature of atresias of the upper two-thirds of the vagina with full development of the internal genitalia. Gemmell<sup>6</sup> was able to find only 14 cases in the literature up to 1926. I have been able to collect 6 other similar anatomic cases besides our own.

Most of the atresias reported are atresias of the hymen, the complete vaginal canal being present. It is interesting to note that Brown<sup>7</sup> collected from the London Hospital 50 cases of congenital retention of menses during a period of twenty-one years. Forty-one of the 50 patients showed the atresia at the hymen, only one near the cervix. Bernstein and Walter<sup>8</sup> reported 19 patients with hematometra, in the twenty years from 1917 to 1937, admitted to the Mount



Sinai Hospital, New York City, 10 of which were due to hymenal atresia, the rest were acquired postpubertal due to a definite etiology.

Jackson<sup>9</sup> reported a case of a girl 14 years old who had never menstruated and who complained of lower abdominal pain. A rectoabdominal examination revealed a cystic pelvic mass. At the first operation a left salpingo-oophorectomy was performed for a chocolate cyst; four weeks later she was re-operated upon for similar complaints and the uterus was found large and cystic. By dissecting the rectovesical septum, the tense mass was encountered and incised with escape of old blood. Jackson believes the hematometra was present at the first operation.

Mayer<sup>10</sup> reports a case of a girl 18 years old who had never menstruated and complained of lower abdominal pain. The hymen was open, the vagina extended for 2 cm., and rectal examination revealed the uterus to be enlarged. At operation the uterus at the lower half was distended and a supravaginal hysterectomy was performed.

Gillespie and Davison<sup>11</sup> report a case of a girl 13 years old who had never menstruated and who complained of lower abdominal pain. Rectoabdominal examination revealed a pelvic mass. A bilateral salpingo-oophorectomy was performed for blood cysts, four months later she was re-operated upon for the same complaints, and a supravaginal hysterectomy was performed for a bulging mass in the lower half of the uterus. After closure of the abdomen the vagina was found to end blindly.

Baer<sup>12</sup> reports a case of a girl 16 years old who had never menstruated. The vagina ended blindly about 2 cm. above the hymen. The rectoabdominal examination revealed a pelvic mass. The rectovesical septum was separated and the pelvic mass opened through the "vagina," with escape of old blood.

Gemmell<sup>13</sup> and Fothergill<sup>14</sup> also reported a case each of hematometra due to atresia of the upper two-thirds of the vagina, for which they performed a supra-vaginal hysterectomy.

#### CASE REPORT

E. D. (76583) was admitted to the Gynecological Service of the Queens General Hospital, Sept. 12, 1938. She was 15 years of age and complained of amenorrhea and lower abdominal pain. Her mother died of pulmonary tuberculosis at the age of 33.

In the summer of 1937 she was suddenly seized with a severe lower abdominal pain which ceased spontaneously after about two hours. At that time she noted a slight swelling of the abdomen. Throughout the year she had about ten intermittent identical attacks at irregular intervals, the last one occurred during the week of Aug. 27, 1938.

Patient appeared about 15 years of age, was poorly nourished, had a poor hemic component and showed multiple acneform eruptions of the skin. In the right lower quadrant of the abdomen there was an orange-sized swelling which was mobile and cystic and seemed to be attached to a pelvic viscus. The external genitalia were normal and the hymen was open. The vaginal introitus admitted the tip of the finger and ended in a blind pouch about 2 cm. above the hymen. Rectoabdominal examination revealed a tense semifirm enlargement of the uterus and the right adnexa were definitely thickened.

Under evipal anesthesia, the vagina was entered for about 2 cm. and by blunt dissection the rectovesical tissue was separated until the full length of the finger could be admitted. No cervix could be marked out. The mass was now clearly defined, being posterior and not filling the cul-de-sac. With pressure on the mass from above, the mass was punctured with a large needle passed through the posterior "fornix" and 1 c.c. of thick dark blood was obtained. The impression was that we had a case of atresia of the upper two-thirds of the vagina, atresia of the external os, effacement of the cervix with hematometra. Four days after this blunt dissection of the vagina, a pneumoperitoneum was obtained which revealed an enlarged mass protruding from the true pelvis and diagnosed as a dilated uterus. She was again examined under anesthesia and a small speculum entered the vagina with ease. Probing for the cervix was a complete failure.

On Sept. 30, 1938, she was taken to the operating room, and under general anesthesia an attempt was made through further dissection of the "vagina" to approach this mass vaginally and to identify the cervix. The line of cleavage through the rectovesical tissue led into and inadvertently ruptured into the free clean cul-de-sac. Pressure from above through the abdomen could not bring this

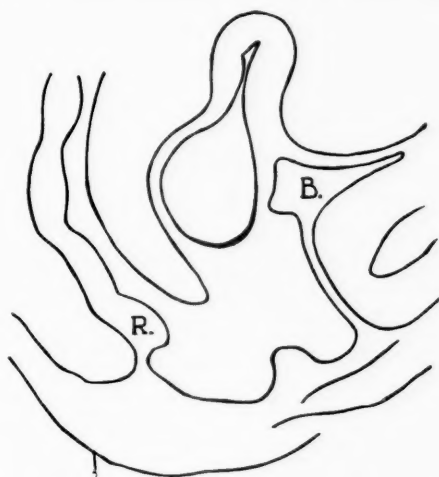


Fig. 1.—Schematic drawing of relations before operation. R, Rectum; B, bladder.

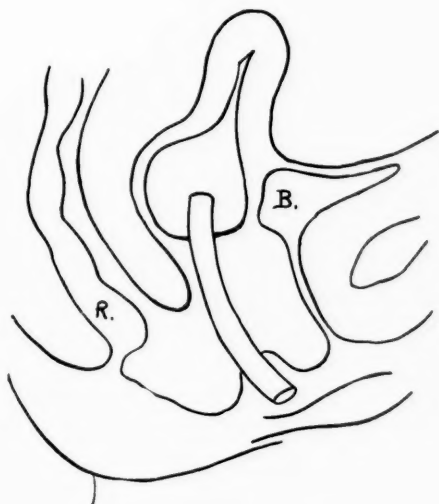


Fig. 2.—After operation.

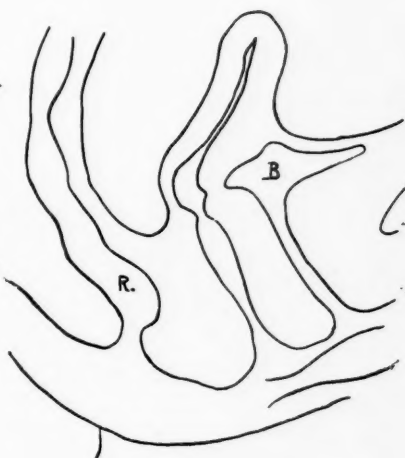


Fig. 3.—End results.

mass down posteriorly to anchor it to the open "fornix" with an attempt to empty this mass through the vagina. The cervix still could neither be identified nor probed.

An abdominal approach was then decided on, which on laparotomy revealed both tubes and ovaries to be normal, the fundus demonstrated no pathology except for a distinct distention of its lower third, especially posteriorly, to about the size of an orange. The cervix as such could not be felt. The bladder was

stripped down from the uterus and a longitudinal incision was made anteriorly and low in the uterus. A finger was inserted through this incision into the fundus and directed downward, meeting with an obstruction which was identified as internal os, and with dilatation of this os there was a back flow of about one-half pint of old blood. The finger in this lower cavity did not identify the cervix nor the external os but rather a smooth dilated cavity below the internal os with most of the bulge posteriorly. An assistant placed a finger in the pre-separated "vagina" and pushed it against the mass which was now considerably reduced. Neither the cervix nor external os could even now be identified. An artery clamp was inserted into the fundus and passed through the internal os and into the apparently dilated cervix. The clamp was pressed against the finger in the vagina. An artificial cervicovaginal fistula was deliberately made and a previously shaped pyrex tube (6½ inch) was passed from above through this cervical vaginal fistula and anchored with two silk sutures. A catheter was then passed from above through the opening in the cul-de-sac into the separated vagina. The abdomen was closed in layers.

#### FOLLOW-UP

The catheter drain was removed in four days, the abdominal skin showed primary healing, and the sutures were removed in seven days. There was some bleeding from the vagina during this time. Eleven days postoperatively the Pyrex tube was removed and the cervicovaginal fistula could now be sounded for about 4 cm.; the cavity above this artificial os apparently did not go beyond the internal os. The pyrex tube was sterilized and reinserted. On the twenty-fifth postoperative day, the pyrex tube was again removed, the cervicovaginal fistula was dilated, and a uterine retention stem pessary was inserted.

Three weeks after the operation she had a profuse period lasting seven days with pre-dysmenorrhea for two days. Three weeks later she again menstruated for four days, being less profuse and associated with co-dysmenorrhea. Since then she has menstruated every twenty-eight days with no dysmenorrhea, periods lasting four to five days, with a moderate flow.

On April 11, 1939, about six months after the operation, she was again taken to the operating room and under anesthesia the stem pessary was removed, the cervicovaginal fistula was found open and permitted a 22 F. dilator to pass with ease, the sound going into the uterus for about three inches. Bimanual examination could not identify a muscular cervix. The thin dome of the vagina seems to make up the cervix. There is complete epithelization of the vagina, permitting the introduction of two fingers. The acneiform eruption of the skin has practically disappeared.

On July 18, 1939, she was again examined under anesthesia, and the cervicovaginal fistula and uterus were again explored. The uterine sound passed up for three and one-half inches; Heger dilators could be passed with ease through the cervicovaginal fistula in sizes 11 to 21 F. As the dilators were passed into the uterine cavity, about 4 ounces of pus were obtained, whose culture was reported negative. At no time has she experienced any fever, abdominal pain, nor dysmenorrhea. The pus was probably encapsulated through the former retention of the stem pessary and had no effect on the physiologic function of the uterus. No cervix can be felt as such but merely the dome of the vagina which forms this cervix. The patient has menstruated regularly since then with no after effects.

#### SUMMARY

1. The fact that the external genitalia and the lower one-third of the vagina were present and normal in the cases of atresia of the upper two-thirds of the vagina, lends clinical proof to the dual origin of the vagina.
2. Whether the atresia of the upper two-thirds of the vagina before puberty is acquired only or both acquired and congenital is still a debatable question. Clinically, most cases seemed to be of the congenital type.
3. The presence of atresia manifests itself by amenorrhea and pain in the lower abdomen after puberty sets in. Our case and those reviewed revealed a dilated lower uterine portion filled with old accumulated blood.

4. The use of a glass rod through the artificial cervicovaginal fistula protruding to the lower end of the vagina prevented the raw vaginal walls from agglutinating. Epithelization of the vagina was complete from the proliferation of the squamous epithelium in the lower third of the vagina. Grafting of intestines or skin is apparently unnecessary to form a vaginal lining. Warton<sup>15</sup> has had a similar experience of epithelization of the vagina without grafting although not known to the writer at the time of the operations.

#### CONCLUSIONS

A girl, who has passed her puberty, who has never menstruated, and who complains of lower abdominal pain, should have a rectoabdominal examination. If this examination reveals a pelvis mass, she is entitled to a vaginal examination, under anesthesia if necessary, to verify its continuity by sounding the vaginocervico-uterine canal before a laparotomy is performed. If the pathology is known before, re-operation for a recurrence of symptoms will be unnecessary, and if the vaginal atresia is first dissected and the operation planned, more conservative surgery will be possible. This patient was left with a uterus, the manifestation of menstruation was established and motherhood was made possible.

Also, extensive operations for an artificial vagina are unnecessary if we let the epithelium from the lower end of the vagina proliferate, thus giving the vagina a normal covering rather than a dry skin or a secreting mucosa.

I wish to extend my thanks to Drs. Walter Kerby and Robert Eckert for their helpful assistance in this case and to Dr. Robert Talisman for his illustrations.

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**Brandstrup, E., and Sindbjerg-Hansen, V.:** On Employment of p-Aminobenzol-sulfonamid in Infections of the Urinary Tract During the Puerperium, Acta obstet. et gynec. Scandinav. 19: 195, 1939.

p-Aminobenzolsulfonamid (streptamid) was employed by the authors in infections of the urinary tract in 120 puerperal patients and given in doses of 60 cg. three times daily. On comparison with 439 other patients with pyelitis, streptamid was found to be considerably superior to other medications.

Streptamid given for four days made the urine microscopically bacteria-free in 73 per cent of the cases. Some of the remaining 27 per cent were given additional treatment for four days, which raised the total percentage of recovery to 88 per cent. Treatment with other medication resulted in a microscopically bacteria-free urine in only 51 per cent.

Streptamid therapy is short, inexpensive and convenient; and it requires no restriction of the diet or daily intake of water.

No dangerous by-effects were noted from this treatment. But since a few instances of disturbances have been reported in the literature, with a dosage similar to the one employed by the authors it is advisable to watch the patients closely during the treatment.

J. P. GREENHILL.

## INTRALIGAMENTOUS GRANULOSA CELL TUMOR

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**I**N AN extensive survey of the literature we have been unable to find any reported case of a granulosa cell tumor of the broad ligament.

R. R., a 37-year-old negress, was admitted to the Cook County Hospital on March 30, 1938, complaining of a progressively enlarging abdomen, associated with stabbing pain in the right lower quadrant, over a period of two months. This pain was more marked when the patient stood erect, and subsided upon reclining. The enlargement was first noted about one year before admission. Except for a period of amenorrhea in March and April of 1937, when the patient first noticed this tumor, she menstruated regularly every twenty-eight days.

During the last year the patient had gained 8 pounds in weight and had become somewhat nauseated and slightly dyspneic on exertion.

The patient was a gravida v, para v. All of the children are living and well, the oldest being 20 years of age and the youngest 12 years of age. Since the age of 12, the patient had been menstruating regularly every twenty-eight days, the menstrual flow being relatively light and of four days' duration. In the past year the menstrual flow was of nine days' duration, with a heavy flow and many blood clots. The period prior to the last one was of seventeen days' duration and was associated with the passage of many blood clots.

The physical examination revealed a well-developed, well-nourished, colored female, about 37 years of age, lying quietly in bed, not acutely ill, and in no apparent pain. The temperature was 98.2° F., respiration 20, pulse rate 96. Blood pressure 120/70. The breasts were atrophic. The heart showed a systolic murmur at the apex. The apex beat was forceful and distinctly visible in the fifth intercostal space in the midclavicular line. A distinct loud second sound was heard over the aortic area. The lungs were essentially negative.

The abdomen showed an eversion of the umbilicus, and a mass arising from the right side of the pelvis, to the right costal margin and above the umbilicus in the midline. It felt smooth and firm and was freely movable. It was not tender on pressure, and definite dullness was elicited on percussion over the mass. Fluid in the abdominal cavity was not made out.

Pelvic examination revealed a normal introitus and the vagina admitted two fingers with ease. The cervix pointed anteriorly and was lacerated and freely movable. The uterus, normal in size, showed a 1 degree retroposition and was displaced to the left. The right adnexal area was the site of a tumor which, on bimanual examination, extended to the right costal arch. The left adnexa were thought to be normal. Hemoglobin, 60 per cent; urinalysis, essentially negative; the blood Kahn, negative.

On the basis of the above findings a diagnosis of a right ovarian cyst was made.

On April 1, 1938, the abdomen was opened through a midline incision. A large cystic tumor mass arising in the right broad ligament was exposed. The right ovary was somewhat flattened by the mass. The left ovary was the size of a small lemon and contained multiple follicular cysts.

A supracervical panhysterectomy was done and the abdomen closed in layers in the usual manner.

Except for a diarrhea which lasted a few days, starting on the sixth post-operative day, the patient made an uneventful recovery and was discharged



seventeen days after her operation and started on a course of x-ray treatments, as a prophylactic measure against possible recurrence.

#### PATHOLOGIC REPORT

The specimen consisted of a uterus amputated above the cervix, both Fallopian tubes, both ovaries, and a large intraligamentous mass. The uterus measured 5 by 6 by 3 cm. The wall was 2 cm. thick. The endometrium was 2 mm. thick and purple gray in color. The fimbriated ends of the Fallopian tubes were patent, the walls thin, and the mucosa pale purple gray. The right Fallopian tube was stretched over and formed part of the upper border of a previously opened cystic mass located in the right broad ligament. The mass (Fig. 1) measured 18 by 15 cm. The external surface was a light pinkish gray to yellowish gray in color and slightly nodular. The surface was traversed by numerous blood ves-



Fig. 1.—External surface of intraligamentous tumor, showing the fimbriated end of the Fallopian tube (A) and the right ovary and suspensory ligament (B).

sels. The wall was up to 4 cm. in thickness. The inner aspect was purplish gray to dark gray in color and in some places was smooth, while in others it was covered by a necrotic membrane. The left ovary measured 8 by 4 by 1 cm. and contained several cysts, the largest being 2.5 cm. in its greatest dimension and filled with a clear fluid. The right ovary measured 4 by 1.5 by 2.5 cm. and, on sectioning, contained a corpus luteum of 1.5 cm. in diameter and several small cysts filled with a clear fluid.

Microscopic sections were made from different areas of the tumor mass and stained with hemalum eosin, Mallory phosphotungstic acid hematoxylin, azo carmine, Gömöri reticulum, Weigert elastica, sudan III, and van Gieson stains. Microscopic study of these sections from different areas of the tumor revealed thin and thick cords of epithelial-like cells (Fig. 2) with indistinct cytoplasmic membranes and round to oval shaped nuclei. The chromatin was distributed in the form of fine chromatin threads with fine chromatin granules deposited on

the threads. Many of the nuclei contained distinct nucleoli (Fig. 3). Mitotic figures were infrequent and in most instances absent. The cords of cells showed irregular trabeculations which were slightly to moderately separated by dense edematous connective tissue strands.

The tumor extended up to and involved the muscularis of the Fallopian tube which was incorporated with the capsule of the tumor (Fig. 4). In places the capsule adjacent to the wall of the Fallopian tube contained groups of tumor cells

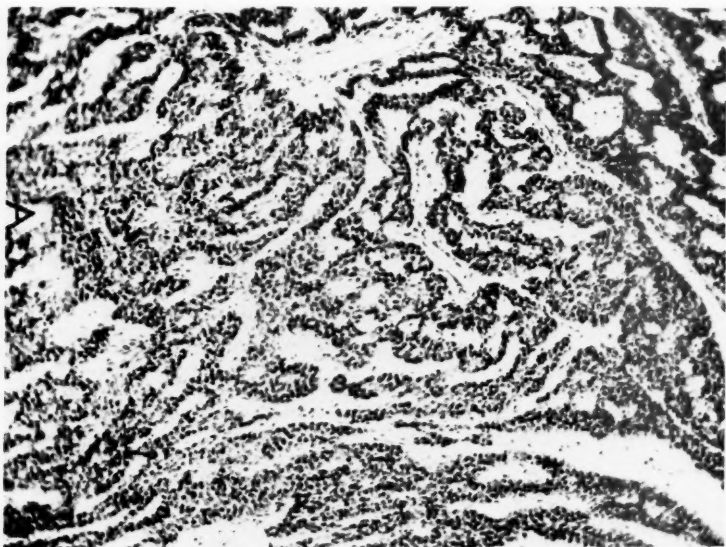


Fig. 2.—Low power magnification  $\times 72$ . Hemalum and eosin stain, showing thin and thick cords of epithelial-like granulosa cells.

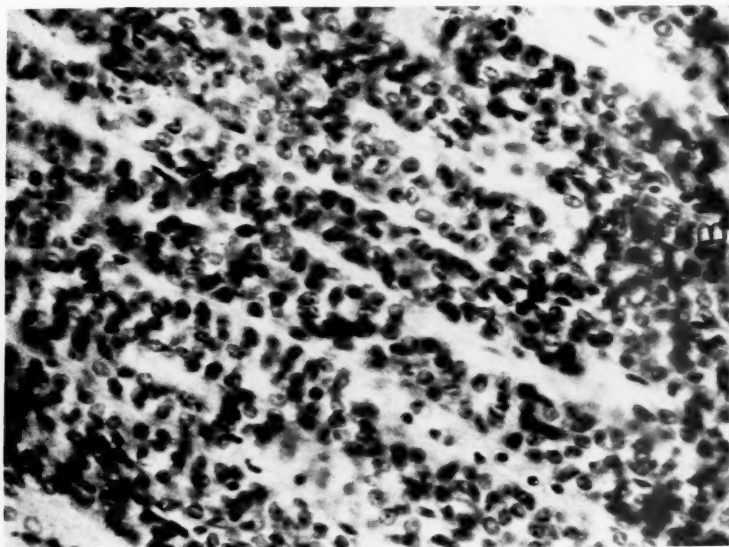


Fig. 3.—High power magnification  $\times 300$ , showing round and oval-shaped nuclei with fine chromatin granules and distinct nucleoli.

arranged in small alveolar-like structures (Fig. 4) with papillary-like proliferations into the lumina of some of these glandlike structures. The nuclear structures of the cells composing these glandular-like bodies were identical with the epithelial-like cells in the trabeculae described above (Fig. 5). The inner aspect of the tumor, which was grossly cystic, was composed of edematous, and in places,



Fig. 4.—Low power magnification  $\times 72$ . Hemalum and eosin stain, showing the extension of the tumor around the Fallopian tube, and group of cells arranged in gland-like structures with papillary proliferations into the lumen.

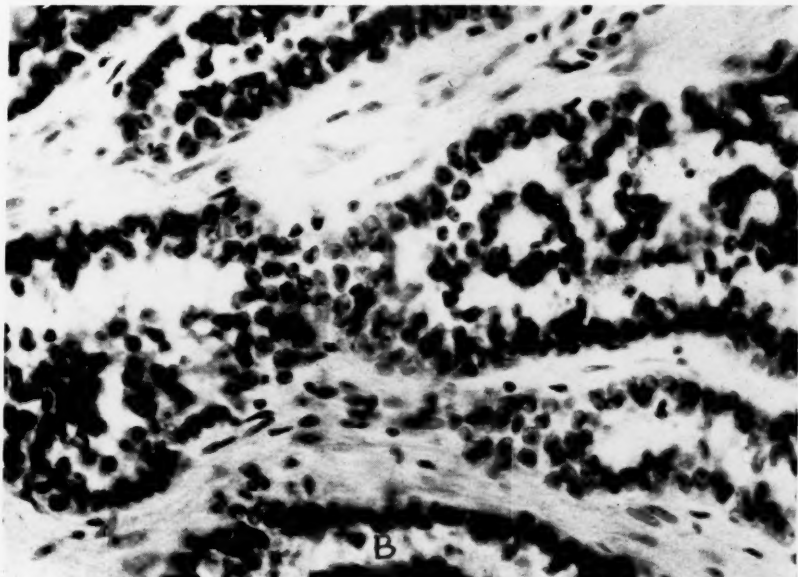


Fig. 5.—Hemalum and eosin stain magnification  $\times 300$ , showing tumor cells in adenomatous structure similar to tumor cells in the cord.

necrotic, connective tissue, infiltrated by many histiocytes containing golden brown pigment granules. The tumor was moderately vascular and contained numerous thin-walled capillaries in the connective tissue bands.

Sudan III stain revealed an occasional tumor cell to contain small sudanophilic droplets in a rather vacuolated cytoplasm. This was particularly noted in single cells which seemed to lie free or border the cords of tumor cells (Fig. 6).

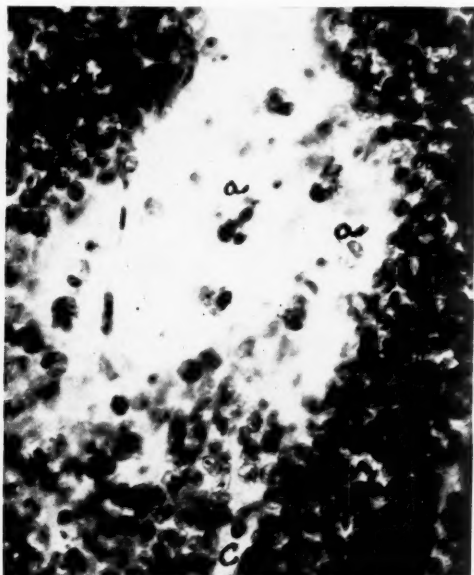


Fig. 6.—Sudan III, magnification  $\times 300$ , showing small darker staining sudanophilic droplets in the cytoplasm of the tumor cells, lying in the free spaces of the tumor and adjacent to the cords of tumor cell (a).

In addition small amounts of sudanophilic droplets were seen in the connective tissue cells. Gömöri stain revealed a large number of reticulum fibrils in the separating strands of connective tissue which, in places, sent fine, delicate branches into the tumor mass, isolating single cells and small groups of tumor cells.

With the above microscopic findings as a basis, we were led to a diagnosis of an intraligamentous granulosa cell tumor.

#### SUMMARY

An intraligamentous tumor in a 37-year-old colored woman is presented which, histologically, reveals trabeculae of epithelial-like cells separated by bands of connective tissue. In addition there are islands in which the tumor appears as small glandlike structures with papillary-like processes into the lumen. This places the tumor in the category of the transitional type or mature trabeculated, mature solid type of granulosa cell tumors. This diagnosis is substantiated by the clinical course presented in this patient, as discussed above. The site of the tumor can be explained by the presence of an aberrant ovary or misplaced mesenchymal rests, having the potentiality of forming granulosa cells.

## INTESTINAL OBSTRUCTION DUE TO MALIGNANCY COMPLICATING PREGNANCY

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THE literature contains many reports of isolated cases and collected series of pregnancies complicated by intestinal obstruction and paralytic ileus. The symptoms and objective findings in total occlusion are readily recognizable. This cannot be said of partial occlusion in pregnancy.

The similarity of symptoms found in intestinal obstruction and those commonly associated with pregnancy often confuse the true diagnosis. This is especially true of the partial, recurrent, and intermittent types of ileus. Constipation, an important diagnostic factor in intestinal occlusion is usually present in pregnancy. Distention, the consort of constipation, may appear quite early. Vomiting, a cardinal symptom of ileus, is commonly associated with pregnancy, and pain is often mistaken for the onset of labor.

Although intestinal occlusion associated with pregnancy is not unusual, the occurrence of ileus in pregnancy caused by carcinoma of the bowel and adnexa is quite rare. This infrequency may be ascribed to the fact that malignancy, especially of the bowel tract, is not commonly associated with the active child-bearing age. In the last century only five authenticated reports of such cases have appeared in the medical literature. To these I add two more. One of these occurred on the service of Dr. Charles A. Gordon, at St. Catherine's Hospital, Brooklyn, and the other on my service at the Caledonian Hospital.

CASE 1.—J. G. (No. 461-37), 23 years old, primipara, was seen at home for the first time on the night of March 16, 1937. Two days previously she had returned from a hospital where she had gone one week earlier to seek relief from abdominal distention, constipation, and inability to retain food. She had been followed in the antenatal clinic of this hospital. The findings at this time were "distended tympanitic abdomen. Expression of pain and tenderness over sigmoid colon. Fecal mass palpable. Patient constipated eight days. Low enemas given to break up masses. Patient left hospital to return home, relieved."

There was a history of seven and one-half months' amenorrhea, her last menstrual period being July 15, 1936. Menstruation began at 13, every three weeks, lasting three and one-half days, moderate flow associated with pain. Both parents, 3 brothers, and 3 sisters were living and well. Aside from measles in early childhood, she was never ill until one month prior to her present complaint. At that time she noted she had become extremely constipated, for the relief of which she had entered the hospital. She told me that two days ago the abdominal distention returned and she vomited a clear fluid. The vomitus seemed to be only the liquid she drank, and there was no odor. There was an occasional slight cramp. There was no history of any previous pelvic inflammatory disease or attack of appendicitis. She had not felt any fetal movement in three days.

Physical examination revealed a young, robust woman who did not appear acutely ill. Her tongue was moist and clean. Temperature was 100° F., pulse 88. The abdomen was markedly distended and tympanitic in all except the right lower quadrant, which was occupied by the pregnant uterus. No fetal heart sounds or fetal movements were obtained. Borborygmi was absent. Fetal head seemed forced into the inlet. The cervix and fornices were devoid of any palpable pathology. Rectally, aside from the fetal head, no other masses could be palpated.

That night she was admitted to the Caledonian Hospital. A flat-plate roentgenogram showed "... Intestinal loops displaced upward and very markedly distended. ... The dilated loops extend into left lower abdomen where the distended outline of the gas filled descending colon ends abruptly. No unusual abdominal opacities are demonstrable. ..." (Fig. 1.)



Colonic and Wangenstein irrigation relieved the distention considerably and flatus was passed freely and abundantly. The nausea ceased. In the morning barium enema x-ray (Dr. W. E. Howes) showed "... Barium filled the rectum, passed through the sigmoid to its proximal third where an obstruction was encountered. An increase in the pressure of the barium column resulted in some overdistention of the rectum. Only a very small amount of the barium passed the point of obstruction, which lay in the left iliac fossa. The barium proximal to the obstruction, appeared to pass into a very narrow channel, perhaps 3 inches or so in length. Palpation of the abdomen was unsatisfactory due to the distention. Patient was rotated to right and left lateral position without any change in the appearance of the barium at the site of the obstruction. ... The



Fig. 1.—X-ray; flat-plate. Marked distention of transverse and descending colon. The distention ends abruptly at the sigmoid. The fetal spine is acutely angulated.

narrow channel proximal to the point of obstruction and the lack of widening of the lumen at the actual point of obstruction suggested an obstruction due to an annular lesion partially obliterating the lumen. ... The fetal breech was sharply angulated and the fetus thought to be dead" (Fig. 2).

Medical induction, using 4 c.c. of quinine-calcium intravenously, followed at hourly intervals by 3 c.c., 2 c.c., and 1 c.c. of the same solution intramuscularly, was begun at 8:45 that evening. By 2:30 A.M. March 18, labor had started, the cervix was 2 cm. dilated. In order to shorten labor a No. 3 Voorhees bag was introduced at this time. By 9:30 A.M. the bag was expelled and soon thereafter labor ceased. Another cycle of calcium-quinine was given and the membranes were ruptured. The fetal heart was not heard for the first time. She was delivered spontaneously of a live male infant weighing approximately 2,100 Gm.

The site occupied by the uterus was immediately filled with distended bowel. Within a short while her tongue became dry, distention increased, and pain set in. Her general condition was aggravated. With the aid of the Wangensteen irrigation and hypertonic intravenous glucose therapy she improved. The distention was soft throughout except in the left lower quadrant where a hard, solid tender mass was now easily felt. Flatus was passed freely and the distention was considerably reduced. Under gas-oxygen-ether anesthesia, a laparotomy was performed. There was free straw-colored fluid in the peritoneal cavity. The transverse and descending colon was distended but not so large as to offer any trouble with the operative procedure. In the left lower quadrant, matted in a mass the size of a fist, were the lower portion of the descending colon, upper portion of the sigmoid, the left tube, ovary, round ligament and the cornu of the uterus.



Fig. 2.—X-ray; barium enema. The rectum and lower portion of the sigmoid are distended with barium, which can be seen trickling through the narrowed lumen into the descending colon. The fetal spine is sharply angulated.

The mass was readily mobilized and exteriorated. The abdomen was closed. The patient's condition was poor although she responded to intravenous glucose therapy and Wangensteen irrigation. Eight hours later she died.

A complete autopsy was unobtainable but the exteriorated mass was removed immediately post mortem. The pathologist's (Dr. W. W. Hala) report: "The abdominal fluid: Direct smear showed innumerable leucocytes, mostly lymphocytic, an occasional red cell. No neoplastic cells were found."

The Tumor Mass (Gross).—Specimen was resected portion of large gut about 4 inches in length. It was slightly bent on itself. The lumen was almost entirely obliterated by a tumor which not only encircled the gut but had thickened its wall eccentrically by invasion through the submucous, muscular, and serous coats.

*Histology.*—Section of wall showing presence of a tumor which originated in the mucosa, infiltrated beneath and through the underlying coats, including the serosa. The tumor was adenomatous in structure and retained the architecture albeit in

a disorderly manner in most of the areas. Tube and Ovary: These were both the seat of tumor of the same histologic structure as that observed in the intestines. There were a number of other sections likewise invaded by the adenocarcinoma, but showing no specific normal histologic structure. Their identity was not definitely established.

*Diagnosis.*—Adenocarcinoma of large intestine with extension to tube, ovary, and pelvic tissues.

Additional laboratory and clinical data: The temperature was normal except for the day of admission when it was 100.4° F. and just prior to her demise when it rose to 109° F. The pulse ranged from 82 to 140 and her respirations were never over 30.

Blood pressure ranged from 144/94 down to 120/80.

The catheterized urine showed 4-plus albumin and sugar, as well as acetone and a few granular casts.

Blood chemistry: Urea 38 mg. per 100 c.c., urea nitrogen 17.7 mg. per 100 c.c., creatinine 2.01 mg. per 100 c.c., chlorides 460 mg. per 100 c.c.

Obviously the annular carcinoma of the bowel antedated the pregnancy. When the uterus and adnexa became abdominal organs, they soon came to lie in direct apposition with the cancerous sigmoid and descending colon. Peritoneal irritation and reaction soon took place and a firm union was formed. From this point both the occlusion and the extension of the growth advanced rapidly.

CASE 2.—R. McG, white, 36 years, gravida iii, para ii, and now six months pregnant, was admitted to the service of Dr. Charles A. Gordon, St. Catherine's Hospital, Jan. 2, 1937.

There was a history of vomiting, abdominal distention and constipation of one week's duration. Her present illness began suddenly on Dec. 27, 1936, when abdominal distention appeared. Shortly thereafter vomiting, about twice daily, set in and recurred up to the day of admission. The vomitus was green and foul smelling. Constipation, requiring enemas, appeared about four days before admission. The last few enemas were ineffectual. The distention gradually increased.

Other than an appendectomy her past history was entirely negative.

Examination revealed an actually ill gravida with pinched facies, dry tongue, temperature 99.3° F., pulse 112, blood pressure 162/94. Urine showed 4-plus acetone; blood count was essentially normal; blood chlorides, 495. The abdomen was markedly distended. The uterus was felt at the umbilicus; fetal heart rate 144 in the left lower quadrant.

X-ray of abdomen revealed a fetus, six months in size. There was marked gaseous accumulation limited to the small intestines.

Despite enemas, gastric lavage and intravenous glucose therapy, the vomiting and obstipation continued. Surgical consultation (Dr. John Scannell) confirmed the diagnosis of intestinal obstruction.

At operation on Jan. 4, 1937, the abdominal cavity was found to contain a large amount of sanguineous fluid. The omentum was thick, hard and studded with nodules. The small intestines were flaming red and quite distended. A large indurated mass was felt in the sigmoid, evidently the cause of the obstruction. The fluid was evacuated, a biopsy of the omentum obtained, and a cecostomy performed.

Twenty-four hours after the operation the patient went into labor and spontaneously delivered a live 3 pound 2 ounce premature infant, who died in twenty-four hours. The patient rallied and was discharged on the sixtieth postoperative day. The cecostomy was functioning well. At home, however, her condition became worse and she died two months later, from cachexia and terminal bronchopneumonia.

The postoperative diagnosis was: (1) Pregnancy six months, (2) intestinal obstruction, and (3) carcinoma of the sigmoid with omental metastases.

The pathologist's report of the biopsy was metastatic adenocarcinoma of the omentum.

Because of the paucity of instances of malignant neoplasm causing ileus in pregnancy, the recorded cases are herein abstracted.

## SUMMARY OF RECORDED CASES

1. C. Maygrier<sup>1</sup> in February, 1879, reported the first case to the Anatomical Society of Paris. She was a 41-year-old decipara about four months pregnant. With each of her last three or four pregnancies she would become markedly constipated. By the end of the fourth month this would be spontaneously relieved. This time in addition to the constipation, rectal tenesmus, loss of weight, and strength appeared. One week before admission to the hospital she took a powerful purgative. This was followed by severe colic and the sudden passage of a very large amount of fecal matter through the vagina. The vulva and vagina were covered with feces, inflamed, and painful. The cervix was soft, closed, immobile and pushed against the symphysis by a large mass thought to be a fibroid in the cul-de-sac. Immediately behind the cervix was a transverse, indurated, fistulous opening into the rectum. Feces passed only by way of the vagina. One month later, bile stained vomiting began and distention, rectal tenesmus, and crises of colicky pain appeared. Diagnosis of partial obstruction was made. Labor was induced by means of holding a finger in the cervix. Immediately after the delivery the obstruction became complete, and the patient died. At autopsy both ovaries were enlarged, cystic, and adherent. About 9 cm. above the anus, on the posterior wall of the rectum and involving the vagina, was a scirrhus carcinoma. Closing the fistulous opening in the vagina was the posterior wall of the cervix, causing complete obstruction after the delivery. Microscopic examination showed adenocarcinoma of the ovaries with secondary involvement of the rectum and liver metastasis.

2. Lotheisen<sup>2</sup> reported the second case in 1894 in the Wiener Klinische Wochenschrift. She was a 44-year-old gravida, with a two-year-old history of obstipation. On admission there was a history of no bowel movement for three weeks. A tumor the size of a fist was felt in the region of the sigmoid. Enemas and laxatives only produced the passage of flatus. Bile-tinged vomiting set in about two weeks later. At operation the left ovary, which was involved in a twisted tumor mass, was removed. The right ovary, which was cystic, was also removed. The colon was released and the bowels moved immediately after the operation. Three weeks later she aborted a five months' fetus. The left ovary was the seat of a carcinoma in association with a dermoid cyst. The right ovary contained the corpus luteum.

3. In 1927, John S. Fairbairn,<sup>3</sup> in an article on "Acute Abdominal Emergencies Complicating Pregnancy and Puerperium" mentions a case of persistent vomiting for which no other cause than her pregnancy could be found. Shortly after termination of the 7½ months' pregnancy, an urgent operation was performed for obstruction from a carcinoma of the colon, that became obvious very soon after the uterus was emptied. No further data are reported.

4. In 1935 LeGac<sup>4</sup> treated a 23-year-old primipara who had been delivered two weeks earlier and who now showed evidence of intestinal obstruction. Throughout her pregnancy she was observed by several obstetricians who were always puzzled by the abnormal volume of her abdomen. The abdomen after the delivery retained its unusual size. At this time she complained of pain, marked distention, constipation and no passage of flatus. Enemas gave prompt relief, but all these symptoms recurred six days later with greater intensity. At operation it was necessary to puncture the bowel and evacuate its liquid contents. An enormous tumor of the right ovary to which the small intestine and the sigmoid were attached was disclosed.

The tumor was an atypical "germinative epithelioma" of the ovary. The patient recovered.

5. Guido Micalè<sup>5</sup> in 1936 reported the case of a 38-year-old terzipara admitted to the hospital unconscious. There was a history of fourteen days' amenorrhea. Five days earlier she was seized with severe, diffuse abdominal pains associated with vomiting and absence of any bowel movement or passage of any flatus. This was promptly relieved. The present attack was identical to the first but without regression of symptoms. Examination revealed a rigid, tympanitic abdomen. There

was a moderate amount of vaginal bleeding. The cervix admitted one finger. The diagnosis was general peritonitis and was possibly due to abortion. She died within twenty-four hours. At autopsy a serofibrinous peritonitis was disclosed, as well as an annular adenocarcinoma of the terminal portion of the ileum with torsion of the ileocecal valve. The uterus showed signs of a recent abortion.

#### DISCUSSION

While it is reasonably simple to diagnose complete intestinal occlusion in the presence of the classical syndrome of cyclic pain, vomiting, constipation, absence of passage of flatus and distention, it is disconcertingly difficult to state with like assurance that occlusion exists when only one or two of the above symptoms are present.

This latter is definitely more difficult in the presence of a pregnancy. In none of the recorded cases are the early symptom-complaints similar (Table I). Only about one-half of the number, 57 per cent, had any vomiting of sufficient frequency to give it any attention, and in only one case was it severe. Two-thirds of the patients presented constipation as a definite complaint and in only one-half of these was it profound. Only one case had severe cyclic pains as an early sign. Five of the 7 patients had some distention worthy of note, while only one of the 7 did not pass flatus.

It was not until occlusion became complete in 4 of the 7 patients that the diagnosis of intestinal occlusion was made. In two the obstruction was complete before delivery. In the other 5, obstruction became complete after emptying the uterus. In all of these, the empty uterus hastened the occlusion either by direct traction or compression.

The records of 6 are complete. Three of the 6 mothers died before leaving the hospital, and one soon after (66 per cent). There is no record of the duration of life in the others. Two of the infants survived (28 per cent).

A definite lesson can be learned from a review of these cases.

1. The existence of partial or intermittent intestinal occlusion should be strongly considered whenever the symptoms commonly associated with normal pregnancy become exaggerated.

2. Drastic purging is dangerous in cases of prolonged constipation.

3. The diagnosis of occlusion due to neoplasm of the bowel, especially in the partially obstructed cases, can be readily ascertained by roentgenogram.

4. Malignancy apparently has little effect on the pregnancy.

TABLE I. SYMPTOM-COMPLAINTS

AUTHOR	VOMITING		PAIN		CONSTIPATION		DISTENTION		ABSENCE OF FLATUS		PALPABLE TUMOR
	EARLY	LATE	EARLY	LATE	EARLY	LATE	EARLY	LATE	EARLY	LATE	
Maygrier		+		++	+++		+	+			+
Lotheisen		+			+++		+				+
Fairbairn	++++										0
Le Gac		+		++		++	+++	++++		++	0
Micale	+	++	+	++	+	++		++	+	++	0
Gordon	+	++				++	++++				0
DerBrucke		++	++		+		+	++			0

5. Recognized in the early months, the pregnancy should be disregarded and the neoplasm treated as under all other conditions. Recognized after viability, the fetus should be delivered from below and laparotomy performed for the correction of the obstruction immediately thereafter.

It is fortunate indeed that these instances are rare.

I wish to take this opportunity to thank Dr. Charles A. Gordon for his interest and the privilege to include his case.



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## ISOLATED PARALYSIS OF THE SERRATUS ANTERIOR MUSCLE DURING THE PUERPERIUM

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THE occurrence of an isolated paralysis of the serratus magnus muscle following generalized infections, exposure to cold or trauma to the long thoracic nerve is not uncommon. Horwitz and Tocantins<sup>4</sup> state that over 150 cases have been reported. The paralysis is more common in men than women and is more frequent on the right than on the left side.

A careful review of the literature reveals only three cases of paralysis of the serratus anterior muscle occurring during the puerperium.

Weber<sup>5</sup> reported the first case in 1880, and in this instance the paralysis was due to puerperal infection. Gowers<sup>3</sup> in 1898 reported a case developing four days after delivery, "excited either by the muscular exertion or exposure of the neck to cold during labor." Berkheiser and Shapiro<sup>1</sup> in 1937 report a case in which they believe the patient injured her right shoulder while pulling on the straps during confinement.

Three additional cases are presented.

CASE 1.—F. B. (Immanuel Hospital No. 62725), white female, aged 20 years, married, para 0, gravida i, had had last menses Jan. 6, 1937. Her expected date of delivery was Oct. 13, 1937. Her pregnancy was entirely normal except that on Sept. 15, 1937, she complained of numbness and tingling in the right arm and hand. These symptoms were transient and disappeared after one week of medication with Brewers yeast tablets, six daily.

The patient was admitted in labor October 6, and after a six-hour labor was delivered by low forceps and episiotomy of a female child, weighing 5 pounds 2 ounces. Anesthesia, open drop ether. On the fourth day, Oct. 9, 1937, the patient complained of pain in the region of the right shoulder which was rather severe but relieved by heat and aspirin. Examination revealed no restriction in motion but the pain was increased on elevation of the arm above the horizontal plane. Under local heat and rest the pain subsided and no deformity of the scapula was noted. On the fourteenth day the patient noted that she could not elevate her arm above a horizontal plane to reach things above her shoulder level. Examination showed definite winging of the scapula. Orthopedic consultation was had and an aero-plane plaster splint advised and refused. Heat, massage, and a high vitamin diet were ordered with arm rest by using a sling support. After six months, complete range of motion was restored, although there was a definite residual weakness of the arm as compared to strength prior to delivery.

She delivered a second child Jan. 26, 1939. The last normal period began May 3, 1938, and the pregnancy was normal until Nov. 28, 1938, when numbness and tingling of the right arm reappeared. The patient was given 6 mg. of thiamin chloride daily with improvement of the symptoms. The delivery was spontaneous and the puerperium normal. Throughout the pregnancy and puerperium there was no change in the condition of the right arm and shoulder nor has there been any change during the sixteen months following delivery.

CASE 2.—K. R. (Immanuel Hospital No. 66888.) The patient, a white female, aged 21 years, was admitted on Sept. 17, 1938, the date of the last menses being Feb. 10, 1938, and the date of expected confinement being Dec. 17, 1938. The patient

was in active premature labor and was delivered of a four pound, nine ounce male child which cried spontaneously and was obviously more mature than the duration of the amenorrhea of the mother.

The pregnancy was uneventful without any signs of toxemia and the labor normal with delivery under cyclopropane anesthesia.

The puerperium was uneventful until September 20 when the patient complained of pain in the right upper arm and shoulder. The pain was intensified upon lifting the arm above the horizontal plane. There was definite weakness of the flexors of the forearm and hand. On September 25 the pain was decreased except on elevation of the arm, and for the first time slight winging of the scapula on the right side was noted. On September 30 the scapula winging was definitely worse, the pain lessened, and all motions free except elevation of the arm above the horizontal.

Search for the cause of the disability was begun and nothing was found except an impacted lower left third molar which was removed. The patient was seen by an orthopedist who advised support of the shoulder by cast; this was refused by the patient. Palliative measures of diet high in vitamin B and rest of the right arm were carried out. The general health of the patient was good, and the baby did well. On Dec. 12, 1938, the patient had a normal period and then amenorrhea. She was admitted to the University Hospital on April 17, 1939.

Following the onset of the second pregnancy, the patient noted soreness and tenderness in the calf muscles of the leg, and numbness in the legs and feet. She also noted some difficulty in keeping her feet warm. There was slight morning nausea and vomiting but it was not severe. Severe headaches, frontal and occipital in character, occurred frequently. Pelvic examination showed an enlarged pregnant uterus in third degree retroversion and flexion. There was a paralysis of the right serratus anterior with inability to raise shoulder above an angle of 90°. The motor power of the legs was somewhat decreased. There was marked pain to pressure over the gastrocnemius group of muscles. Pain and touch reaction were increased over both lower extremities. Reflexes, coordination, and gait were normal.

*Laboratory: Spinal fluid:* Initial pressure 3 mm. Hg and rose to 13 cm. on compression of jugulars. The fluid was clear; cell count 5; protein 7 mg. per cent; Kline negative; colloidal gold curve 1100000000 and sugar 68 mg. per cent.

*Blood:* Serum calcium was 10.5 mg. per cent and the serum phosphorus 5.5 mg. per cent. The hemoglobin was 11.5 Gm.; the red cell count 4,480,000; the white cell count 8,000 with a normal differential.

The patient was given 15 mg. of thiamin chloride daily; 40 drops of oleum percomorphum daily; 5 c.c. of liver extract every other day; 18 gr. of ferrous sulfate daily; and a high vitamin, high carbohydrate diet.

In spite of therapy there was no improvement and a diagnosis of a low grade toxic neuritis of pregnancy was made. After intradepartmental consultation, a vaginal hysterotomy was done on May 9, 1939.

The patient made an uneventful convalescence and within one week of the termination of pregnancy there was noted an improvement in the patient's general physical condition with lessening of leg symptoms and headache.

She was dismissed from the hospital on the fourteenth day greatly improved.

CASE 3.—Courtesy Dr. W. H. Taylor. The patient, a white female, aged 22 years, had had two previous pregnancies. The first was normal, full term, with a normal delivery on Dec. 3, 1936, and followed by a normal puerperium. The second pregnancy ended in a spontaneous abortion in the second month of gestation, on Aug. 28, 1937. She had a normal period beginning Oct. 28, 1938, and after a normal pregnancy was delivered on July 28, 1939, under nitrous oxide and ether anesthesia. The baby weighed 7 pounds and 12 ounces and was normal. On the fourth post-partum day she complained of some pain in the region of the right scapula, but no particular attention was paid to it.

She was seen on Sept. 9, 1939, with a well-established paralysis of the right serratus anterior muscle. She was advised to use local heat and muscle rest with massage. On Oct. 19, 1939, there had been some improvement although winging of the scapula still occurred. The patient's condition has not improved much at the present time.

## DISCUSSION

In all of these cases and in the three cases reported in the literature, the paralysis was on the right side. The three patients presented were all right handed and the more active shoulder was paralyzed. The predilection for right-sided involvement suggests that perhaps the nerves to an active group of muscles are more susceptible to damage, which occurs either as a result of anatomic peculiarities or from deficiency states.

The first symptom is pain in the shoulder region and in all instances it occurred on the fourth post-partum day. The winging of the scapula was not noted until later, and in the one carefully observed case appeared on the ninth day.

The cause of the isolated paralysis of the serratus magnus in the reported cases has two possible explanations. Horwitz and Tocantins claim that a lateral tilt of the head and the neck puts the nerve on tension, with injury to the nerve as it comes across the chest cage. This tilt might occur during anesthesia as the anesthetist frequently tilts the head forcibly to prevent aspiration of regurgitated gastric contents or swallowing of the tongue. Whether this occurred in these cases or not cannot be verified. It would seem that paralysis from this cause might be a more frequent sequel than it seems. Apparently it is very uncommon. The second possible explanation is that the paralysis is a manifestation of an unrecognized vitamin B deficiency or of a recognized deficiency inadequately treated. This latter explanation seems to be most plausible.

In the first case, symptoms of vitamin B deficiency were presented three weeks prior to delivery but they subsided on vitamin B complex therapy. The same symptoms recurred during a subsequent pregnancy but more intensive therapy was used and the paralysis failed to occur.

In the second case no history of vitamin B deficiency was obtainable prior to the onset of the paralysis. A subsequent pregnancy which had its inception three months after the first pregnancy was terminated was complicated by a varied but rather typical symptom syndrome of vitamin B deficiency—in spite of the fact that she had been on a fortified vitamin B diet. Either the amount of vitamin B given was inadequate or there was failure of utilization of the orally administered vitamin.

The treatment consists of muscle rest, preferably in a cast or splint, but if that cannot be done, support and rest in a sling. This should be re-enforced with local heat and massage. The diet must be high in vitamin B content or supplemented with an adequate amount of thiamin chloride intramuscularly.

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## BILATERAL SIMULTANEOUS TUBAL PREGNANCY

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**B**ILATERAL simultaneous tubal pregnancies are of sufficiently rare occurrence to justify reporting any verified case. To the accepted list of 78 cases\* of bilateral simultaneous tubal pregnancies, we are adding an additional case with microscopic proof.

R. McQ., colored, aged 29 years, married, had had three pregnancies; first five years ago, second two years later, resulting in a spontaneous miscarriage, and was delivered of a normal child six months ago (May 21, 1939, Harlem Hospital, New York City). Menarche occurred at 13, twenty-eight-day cycle, duration six days. Last menstrual period occurred on Sept. 25, 1939. No history of venereal infection. No previous operations.

Patient was first seen in the Gynecological Clinic, Nov. 20, 1939, and gave a history of having spotted toward the end of October for one day, accompanied by pains in the lower abdomen and rectum. For the next few days, the patient passed a dark vaginal discharge. For the past three weeks, that is, since the spotting which occurred at the end of October, the pains had persisted. There was no further vaginal discharge, no morning nausea. The pains, however, were becoming more severe.

Examination revealed a distended but flaccid abdomen, very tender on pressure. Bimanual and rectal examinations disclosed bilateral doughy and resilient adnexal masses and a bogginess in the cul-de-sac. The uterus was soft and enlarged, regular in shape, anterior in position. There was no vaginal discharge. A diagnosis of ruptured tubal pregnancy was made and the patient was admitted to the Hospital.

Operation was performed Nov. 22, 1939. Upon opening the peritoneum, free blood and clots were found. The right adnexa were delivered into the incision and a ruptured Fallopian tube was found. The right tube and ovary were excised. Upon examining the left adnexa this tube likewise was found to contain an ectopic gestation and the ovary covered with a clot. This tube and ovary were excised. On Nov. 24, 1939, the patient passed a large uterine cast. The patient made an uneventful recovery and was discharged in good condition from the hospital on the thirteenth day.

Pathologic Examination by Dr. A. Sumner Price: "The specimen consists of two large tuboovarian masses.

"A. The right tube measures about 3.5 cm. in diameter for about two-thirds of its length. It is covered with blood clot and is apparently filled with it. The external appearance suggests an ectopic pregnancy. The ovary shows a large corpus luteum, some edema, and blood clot over the surface. When the tube is incised, on one side is found a portion of degenerated embryo about 14 mm. in length. A yolk-like structure can be recognized. The entire chorionic mass is about 3.5 cm. in diameter. The corpus luteum of the ovary measures about 2 cm. in diameter.

"B. The left tube is dilated to about 3 cm. in diameter in the distal third and is apparently filled with blood clot. The ovary attached shows edema and a large corpus luteum. When this tube is incised, it shows a chorionic mass about 3 cm. in diameter which contains a cystic cavity of slightly irregular outline in the central

\*Fishback, H. R.: AM. J. OBST. & GYNEC. 37: 1035, 1939; Torpin, R.: Ibid. 39: 345, 1940.

area, measuring about 1.5 cm. in diameter. No embryo is found on this side. The ovary shows a corpus luteum about 1.5 cm. in diameter and is slightly cystic. Separately is a mass of blood clot measuring about 4 by 3 cm.

"Microscopic examination of the mass marked 'A' shows a large corpus luteum of the ovary, with numerous immature germinal cells in the cortex. The tube shows



Fig. 1.—Young chorionic villi from "A" (right) tube showing an abundance of trophoblastic cells in the lower half of picture.



Fig. 2.—Young chorionic villi found in tube (left) "B". There is an abundance of trophoblastic cells at the top of the picture. The chorionic villi are slightly more edematous than in "A"; hemorrhage is more marked, but the villi are of approximately the same age.



considerable hemorrhage over the surface. In the interior is found blood clot, chorionic villi, and an abundance of syncytial and trophoblastic cells (Fig. 1). At one point there is considerable hemorrhage and leucocytic reaction in the wall, which suggests rupture at this point. There is also found a portion of embryonic tissue in which primitive neural and enteric elements can be recognized which are forming from a mesenchymal mass.

"Microscopic examination of the mass marked 'B' shows a large corpus luteum of the ovary, with some hemorrhage over the surface. The tube on this side is dilated and contains blood clot, an abundance of chorionic villi, and decidua of pregnancy (Fig. 2). The chorionic villi are of the same general structure and of about the same degree of maturity as those found in the first mass.

"Diagnosis: Bilateral ectopic tubal pregnancy and bilateral corpus luteum of ovary."

### EXTRAOVARIAN GRANULOSA CELL TUMOR

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WITH very few exceptions, granulosa cell tumors are found in the ovary. Voigt<sup>1</sup> has reported a retroperitoneal granulosa cell tumor in a woman past the menopause, in which the histologic structure was characteristic, and from which a biologically active extract was obtained. Compton<sup>2</sup> reports a granulosa cell tumor of the left ovary, with occurrence sixteen years later, in the same patient, of another granulosa cell tumor located in the right vesicouterine fold. It was in no way connected with the right ovary.

A report of a third extraovarian granulosa cell tumor by Ragins and Frankel<sup>3</sup> appears on p. 302, this issue.

The following is a report of an encapsulated, partially cystic tumor situated in the left broad ligament. We believe that there is sufficient evidence to prove that this is a granulosa cell tumor, and that the case is of particular interest because of the extraovarian location of the tumor.

#### CASE HISTORY

Mrs. L. H., a 30-year-old, white married woman was admitted to the Gynecologic Service of the Colorado General Hospital on April 21, 1939.

Menstruation began at the age of ten years. The periods were regular, every thirty days, lasting four days, with little or no pain. At the age of sixteen years she began to have moderate dysmenorrhea. The flow, however, continued normal in amount.

At the age of twenty the patient was married. There soon followed in rapid succession five pregnancies, all of which terminated spontaneously in from three to seven months. There was marked nausea and vomiting throughout all of the pregnancies, and menstruation occurred in normal amounts with but slight irregularity.

The sixth pregnancy continued for eight months, possibly due to bed rest for approximately four months during this time. Three or four times during this pregnancy she menstruated at the time the menses might be expected to occur. This pregnancy terminated at eight months in the birth of a male child which survived.

The patient's husband died after five years, and two years later she married again at the age of twenty-seven. Her seventh pregnancy soon followed and continued for seven months, when she was delivered of a premature female baby which survived.

The eighth pregnancy terminated by spontaneous miscarriage at five months in the Colorado General Hospital in January, 1939. This baby lived for about eighteen

hours. This pregnancy was also characterized by normal menstruation at each regular period. In fact, due to the regularity of the periods, the patient was four months' pregnant before realizing her condition.

Following this miscarriage, the patient first became cognizant of a palpable mass in the lower left abdominal quadrant, associated with bearing down pain. She had become increasingly nervous and irritable. Migraine with which she has suffered most of her life became more frequent and severe.

Aside from three attacks of pneumonia during childhood, and a left otitis media which discharged until a few years ago, leaving marked impairment of hearing in this ear, the history other than cited was negative.

On admission examination revealed a well-developed, fairly well-nourished female of apparently her stated age. She did not appear to be acutely ill and was not in pain. Temperature was 99.2° F., pulse 94, blood pressure 118/76. Red blood count and hemoglobin were normal. White blood count was 12,240 with 66 per cent polymorphonuclears. Urine was negative; Wassermann negative.

There was a large, moderately soft, nonfluctuant mass in the left side of the pelvis, not freely movable. It was apparently not connected with the uterus, which was freely movable and appeared normal as did the right adnexa.

A diagnosis of ovarian cyst, probably cystadenoma, was made.

A low midline abdominal incision was made on April 24, 1939, adequately exposing the uterus, tubes, and ovaries, all of which appeared to be normal.

Lying below the left tube, between the folds of the broad ligament, was a mass corresponding in size and consistency to that found on pre-operative examination. An incision was made in the anterior leaf of the left broad ligament and the mass was easily enucleated by finger dissection. There was no pedicle. The incision in the broad ligament was closed, the appendix removed incidentally and abdomen closed in the usual manner.

The specimen removed consisted of an encapsulated spheroidal tumor measuring 10 by 7 by 5 cm. Externally it was grayish red and coarsely nodular, with a row of adipose and fibrous tissue tags along one surface.

Two days later, due to the apparent nature of the tumor, a light curettage was done in order to obtain a specimen of endometrium for study.

For eight days following the operation there was uterine bleeding, usual after removal of granulosa cell tumors. Aside from this the postoperative course was uneventful.

It had not been possible to examine this patient since her discharge from the hospital. However, in a personal communication received on Dec. 14, 1939, approximately eight months after removal of the tumor, she stated that her health was better since her operation, but that she was pregnant and had pain in the left side at times. She had menstruated three times since the operation; on June 3, 5 days; July 3, and August 3, each one day.

In a subsequent communication, Dr. G. L. Robinson of Salida, Colorado, states that he delivered this patient at term on Feb. 20, 1940, of a normal female baby weighing 6 pounds and 9 ounces. The mother reports that the baby is normal, that she is nursing it and that her own health is better than before.

From the above case history it is evident that genital function has been abnormal, but the history is not that of a typical granulosa cell tumor, with which, in the child-bearing period, one would expect a history of amenorrhea or anovulatory menstruation with more or less profuse metrorrhagia at irregular intervals. Because of the atypical history, it is necessary to assume that the tumor, being of the diffuse or sarcomatoid type, produced relatively little estrogenic hormone and that the amount produced was insufficient to inhibit normal follicle maturation and ovulation. The endocrine effect of the tumor, although comparatively slight, may have been sufficient to interfere with the course of the patient's pregnancies.

*Pathologic Report.*—The tumor was spheroidal, fully encapsulated, and as above stated in size and external appearance. It was composed of pale yellowish gray soft tissue, containing many cysts, varying from 0.1 to 3.0 cm. in diameter. The cysts had a smooth lining and contained clear or slightly turbid watery fluid (Fig. 1).

Microscopically, the tumor was made up of irregularly shaped fusiform cells with large coarsely reticular nuclei and scanty eosinophilic cytoplasm. These cells were supported by a delicate connective tissue reticulum containing numerous capillary blood and lymphatic vessels. The arrangement of the tumor cells varied some-



Fig. 1.—Polycystic tumor from the left broad ligament.

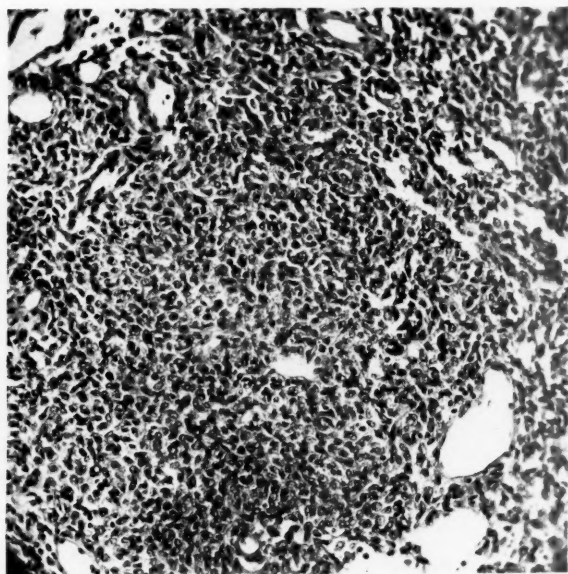


Fig. 2.—Granulosa cell tumor. Partially cystic zone.  $\times 140$ .

what in different regions, but, in general, the cells lay in small compact whorls and interlacing bundles. This arrangement suggested that of normal ovarian cortical stroma. Throughout the tumor there was alternation of densely cellular zones and loose areolar connective tissue. Fusiform tumor cells extended outward from the denser zones into the areolar tissue along the intercellular fibrils.

The cysts were situated in the denser zones and had no epithelial lining. Tumor cells formed the walls. The cysts might be emptied or filled with faintly eosinophilic granular material (Fig. 2).

In the densely cellular zones some of the centrally located cells were hyperchromatic, with bizarre nuclear forms and occasional mitotic figures. Small groups of cells in such zones had a folliculoid arrangement, but Call-Exner bodies were not seen (Fig. 3).

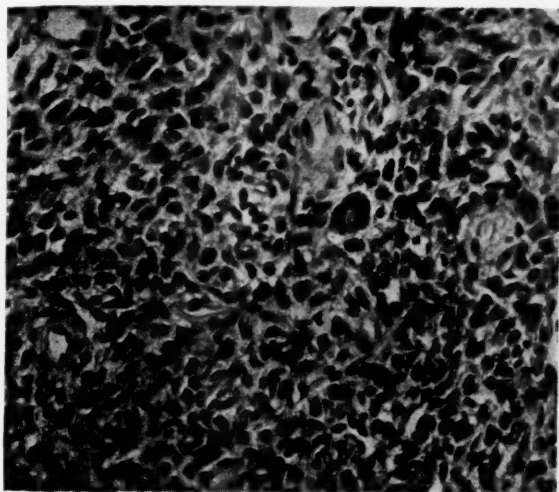


Fig. 3.—Granulosa cell tumor. Solid zone.  $\times 200$ .

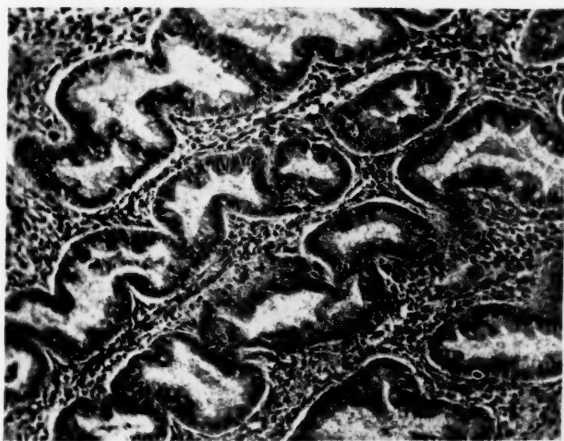


Fig. 4.—Specimen of endometrium showing glandular hyperplasia.  $\times 140$ .

Small collections of lymphoid cells were present in the tumor, situated in perivascular connective tissue, and scattered leucocytes, chiefly lymphoid, lay between the tumor cells.

Histologic examination of the endometrium revealed closely grouped, moderately tortuous, endometrial glands with tall columnar basophilic epithelium, in some instances infolded. The lumina of the glands contained pink-staining granular precipitate and occasional leucocytes and erythrocytes. The endometrial stroma was made up of small darkly-stained fusiform cells and was edematous, with small hemor-

rhagic zones in the superficial portion. Surface epithelium was not present, evidently having been desquamated together with a portion of the underlying endometrium (Fig. 4).

#### DISCUSSION

Comparison of this tumor with the one reported by Eastlake<sup>4</sup> in 1931 shows close similarity in structure. It is noteworthy that Eastlake's patient, a child aged three, developed *pubertas praecox* although the tumor was of the relatively undifferentiated diffuse (sarcomatoid) type.

No biologic assay for estrin content of the patient's urine or blood, nor of the tumor tissue was attempted, because the nature of the tumor was not suspected until after its removal and fixation. In this connection it should be mentioned that in patients in the child-bearing period, biologic assay is of less value than might be expected as the amount of estrin present may vary widely within normal limits (Gustavson and others,<sup>5</sup> Dworzak and Podleschka<sup>6</sup>).

The extraovarian location of this tumor is an important feature of the case. Extraovarian granulosa cell tumors are rare, only two having been previously reported, but are of great interest from the viewpoint of histogenesis.

In embryonic life the gonads of both sexes develop from the genital fold. In the female it has been long thought that the follicular lining cells are derived from the "germinal" epithelium covering the surface of the genital fold at the ovarian site. The germ cells have been thought also to migrate inward from this epithelial layer.

Fischel's<sup>7</sup> embryologic studies indicate that this is not true, but that the germ cells originate in the entoderm, and migrate into the mesenchymal zone of the germinal ridge where the surrounding mesenchymal cells differentiate to form primordial follicles. According to Fischel's concept the power of forming an organ (ovary) is originally possessed by the mesenchymal cells in a large area which is gradually restricted to a narrower field, which in turn ultimately becomes the gonad. However, the mesenchymal cells beyond this field retain a potentiality for differentiation, if stimulated to development. Variation in histologic structure in granulosa cell tumors is probably dependent upon the stage of differentiation of the tumor cells toward the adult granulosa cell form, and explains why, in the words of Schiller,<sup>8</sup> "The tumors when unripe have the character of connective tissue, and when ripe show epithelial structure." Thus undifferentiated but potentially specific granulosa cells may remain in the territory originally occupied by the genital fold. In the adult this zone extends retroperitoneally from the region of the adrenal to the cortex of the ovary. It is in this area that extraovarian granulosa cell tumors may be expected to occur.

Granulosa cell tumors of the ovary are commonly believed to originate from granulosa cell rests, although some authors have found evidence that such tumors may be derived from previously normal follicular lining cells. Butterworth,<sup>9</sup> on the basis of experimental irradiation of the ovaries of senile mice, found granulosa cell tumors apparently developing from normal follicles following degeneration of the ova. Robinson<sup>10</sup> in 1930, on the basis of four cases reported by him, claimed that the granulosa of the follicles is the genetic source of granulosa cell cancer. In one of his cases he believes that tumor growth from follicular lining can be traced. In this case, however, there were changes in the voice and hair distribution, with hirsutism suggesting masculinization.

Dockerty and MacCarty<sup>11</sup> in 1939 reported a case of granulosa cell tumor in which origin from follicular epithelium is considered probable by the authors. Many follicles which appeared otherwise normal presented localized hyperplasia of the granulosa cells with extension to involve surrounding tissue.

While origin from follicular lining cells within the ovary is debatable, such origin in an extraovarian tumor would be unlikely. Origin of the tumor from a granulosa cell rest of mesenchymal derivation seems to be a more reasonable conclusion, and is supported both embryologically and by the sarcomatoid appearance of the tumor cells.

#### SUMMARY

A case of extraovarian granulosa cell tumor is described. It is believed to be clinically benign. There is evidence that the tumor caused disturbance of genital



function with endometrial hyperplasia and repeated abortion or miscarriage. The patient's only normal full-term pregnancy occurred after surgical removal of the tumor. Histogenesis of the tumor is discussed.

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## SPONTANEOUS RUPTURE OF THE SPLEEN COMPLICATING LABOR

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**T**RAUMATIC or spontaneous rupture of the spleen is not an uncommon occurrence in the nonpregnant state. However, rupture of the spleen occurring spontaneously during pregnancy, labor, or the early puerperium is quite unusual, almost rare enough to be called a medical curiosity. Because of this rarity, difficulty in diagnosis, and rapidity of death, most cases are not recognized during life and are discovered only at autopsy.

*Etiology.*—In more than half of the reported cases of splenic rupture complicating pregnancy, there is a definite history of trauma. In the group classified as spontaneous rupture the etiologic factors are still obscure. Certain factors, however, may be considered. Walton<sup>1</sup> has stated that splenomegaly accompanied almost every case of spontaneous splenic rupture recorded in the literature. Therefore, it seems that from an etiologic standpoint the question revolves around the cause of the accompanying splenomegaly. From the literature 9 cases of spontaneous splenic rupture were collected. Seven of these showed varying degrees of splenomegaly, and in only 1 case (case of Hubbard) was there a definite pathologic reason, malaria.

The question as to whether or not uncomplicated pregnancy might in itself be the cause of physiologic enlargement of the spleen has been entertained by previous writers. Kotschnew and Manenkow<sup>2</sup> believe that in pregnancy the splenic pulp may proliferate causing enlargement of the organ. De Lee<sup>3</sup> states that the spleen increases somewhat in size during pregnancy. Dameshek<sup>4</sup> points out that the spleen observed after death often gives an erroneous idea of its size, and when it is observed in the human being at operation, the spleen is a much larger organ, varying normally in size from 250 to 350 Gm.

On the other hand Barcroft and Stevens<sup>5</sup> have shown in the dog and other laboratory animals that the size of the exteriorized spleen varies during pregnancy and that it probably reaches its smallest size a few days before labor. They attribute this shrinkage to the need for supplying blood to meet the increased capacity of the vascular bed caused by dilatation of the uterine vessels.

Serbin<sup>14</sup> in a recent report comments, "Pregnancy does not cause the spleen to undergo any appreciable hypertrophy, any enlargement is due to pre-existing disease." Further he adds, "Splenomegaly is sufficiently rare complicating pregnancy to warrant the addition of all observed cases to the literature."

The effect, therefore, of pregnancy as an etiologic factor of splenomegaly in the human still remains a moot question.

Unquestionably in the presence of an enlarged friable spleen the most minimal internal trauma, often unrecognized, may cause rupture. Klotz in discussing Kehr's<sup>6</sup> case believed the indirect action of force to be analogous to the coup and contracoup injuries sustained in skull fracture. In this manner an abrupt change of position or the sharp contraction of the abdominal musculature and the uterus accompanying bearing down may push the spleen against the left lobe of the liver or the costal margin, causing rupture.

Pathologically two types of rupture are discernible. The most common is the complete tear involving both the parenchyma and capsule. The other type may be called an incomplete rupture and involves the parenchyma alone, causing the formation of a subcapsular hematoma. This type probably accounts for the classic signs and symptoms of early rupture, and only when the capsule is ruptured does intra-abdominal hemorrhage with signs of shock intervene. If the condition is not recognized early, with the institution of proper shock therapy followed by immediate splenectomy, death rapidly ensues.

As far as I could ascertain this is the first case of spontaneous splenic rupture complicating labor reported in the American literature.

In 1925, Stretton<sup>7</sup> reported a case with recovery that had come to operation diagnosed as ruptured ectopic gestation. Kotschnew and Manenkow<sup>2</sup> in 1930 reported 14 cases collected from the literature to which they added a fatal case of their own. Bohler<sup>8</sup> in 1932 added another case. Two cases appeared in the British journals reported by Smith, Morrison and Sladder<sup>9</sup> in 1933, and by Burnett and McMerrimey<sup>10</sup> in 1935. Since then two other cases have appeared in the German literature, recorded by Sommer<sup>11</sup> in 1937 and R. v. Hoch<sup>12</sup> in 1938.

#### CASE REPORT

Mrs. M. R. (Case 137220), a 34-year-old, white multipara, was admitted to the Obstetrical Service of the Cincinnati General Hospital on Jan. 24, 1940 with a history of slight vaginal bleeding and ruptured membranes.

Her last period occurred June 19, 1939. She was a patient in the prenatal department of this hospital and had been attending the clinic regularly. Her pregnancy progressed normally up until four days before admission when she developed a slight upper respiratory infection. Two days prior to admission the patient noticed slight, painless vaginal bleeding. This continued intermittently until her membranes ruptured spontaneously on the day of admission.

*Past History.*—Essentially negative except for the usual childhood diseases. She gave no history of malaria or typhoid fever, and did not use alcohol in any form. Catamenia occurred at 14, periods regular every twenty-eight days, lasting from three to four days.

She had been married for the past thirteen years, had had 6 pregnancies including the present; two children living and well, and three children dead (two in the neonatal period, 1 at 6 months, cause unknown).

On admission, temperature was 100.6° F., pulse 80, respirations 20, blood pressure 125/70. Blood Wassermann, Kahn test and urinalysis were negative.

Physical examination revealed only slight evidence of acute upper respiratory infection and heart and lungs were normal. Obstetric measurements were adequate. Uterus was at term, presenting part floating, back on the left, fetal heart rate 134 and regular. Rectal examination revealed a long, soft cervix, 1 finger dilated. Since the patient was not in labor, she was sent to the ward and isolated.

Patient soon became temperature free, congestion of the nose and throat cleared and she was apparently well. A medical induction was attempted three days after admission but without results. On January 29 patient had a severe chill, lasting for twenty minutes, temperature 104° F., pulse rapid but of good quality. Patient offered no subjective complaints of any kind. Red blood count, 2,600,000; white blood count, 13,000; Hb, 10 (Sahli). Examination of the chest revealed a few diffuse rales at the right base. The emergency chest plate revealed no ab-

normalities. Fluids were forced and the temperature dropped below normal at 8 P.M. The blood pressure at this time was 120/80, pulse 85 and regular.

A few minutes after midnight, Jan. 30, 1940 the patient commenced to have regular uterine contractions. Rectal examination revealed a soft mass presenting, presumably a breech. Fetal heart had not been heard since early afternoon. At 1:40 A.M. the cord prolapsed, but since no pulsation was felt, and the fetal heart had not been heard for several hours, interference was not contemplated. About five minutes later the patient delivered a stillborn white male, weighing 2,069 Gm. Pituitrin was given, and the placenta was expressed intact with more than normal bleeding. Patient continued to bleed in spite of intravenous ergot and uterine massage. The cervix was examined but no lacerations were found. The uterus was immediately packed through a tubular packer. Since the patient showed signs of mild shock, 750 c.c. of glucose and saline were given, followed later by a transfusion of 500 c.c. of whole blood. She rallied rapidly and left the table in good condition; blood pressure 130/80.

At 3 A.M. the patient again went into shock. Fluids were started and another 500 c.c. of blood were given. Blood pressure 84/48, uterus was well contracted, and there was no discernible bleeding through the pack. The shock deepened and the patient did not rally. She complained only of numbness of the lower extremities. At 6 A.M. the patient was still in shock and showed signs of early pulmonary edema. About the same time slight abdominal distention was noted accompanied by lividity of the lower half of the body. Oxygen therapy was started and respiratory stimulants given. Death occurred at 10:50 A.M.

*Post-mortem Examination.*—(Dr. Abraham Fink, Department of Pathology, Cincinnati General Hospital.)

*Anatomic Diagnosis:* Rupture of the spleen with hemorrhage into the peritoneal cavity. Focal hemorrhages into the lower lobe of the right lung, mesentery, fundus of the stomach, and colon.

*Gross Description:* The autopsy was performed four hours post mortem. The abdominal cavity contained 600 c.c. of dark red fluid blood. The peritoneum was smooth, glistening, and pearly pink. In the upper right quadrant there was a thin fibrinous deposit on the under surface of the diaphragm and on the spleen. The organs were in their normal relationship and the large, firm uterus was intact and extended superiorly to 2 cm. below the level of the umbilicus. The heart, aorta, and lungs appeared normal except for scattered areas of hemorrhage, varying from 0.5 to 1.5 cm. in diameter in the right lower lobe of the lung. In the substance of the left diaphragm there was a circular area of hemorrhage 1 cm. in diameter.

The large, soft, opalescent red spleen weighed 625 Gm., and was covered with smooth glistening capsule. At the notch of the anterior border of the spleen there was a shallow groove extending along the diaphragmatic surface. About the midpoint of this groove there was a ragged, linear break in the capsule, measuring 1.5 cm. in length and 0.3 cm. in width. This extended for a depth of 1.2 cm. into the parenchyma of the organ. There were a few light, fibrinous strands lying on the surface of the spleen but not adherent to it, except in the region of the break. Sectioning revealed a dark, pultaceous splenic tissue.

The dark, reddish brown liver weighed 2,050 Gm. On section the tissue was brown, firm, and dripped blood. The gall bladder and pancreas were normal.

The mesentery of the small intestines contained several circular areas of hemorrhage which varied from 0.5 cm. to 1.5 cm. in diameter. Several circular areas of hemorrhage 0.5 cm. to 2.0 cm. in diameter were present in the wall of the fundus of the stomach and colon.

The kidneys, ovaries, and oviducts were apparently normal. The uterus was large, firmly contracted and measured 21 cm. by 8.3 cm. The walls were firm and pink, were intact, and measured 4 cm. in thickness. The cervical os was patulous but not lacerated. The endometrium was slaggy and dark red, and the fundus was covered by grayish stringy material.

*Microscopic Diagnosis.*—Acute passive congestion of the lungs, liver, and spleen; focal hemorrhage in the lungs and stomach; toxic hepatosis and nephrosis; recently post-partum uterus.

*Microscopic Description:* Sections of the spleen showed sinusoids markedly dilated and engorged with erythrocytes and polymorphonuclear leucocytes. In some areas the walls of the sinusoids were disintegrated with the formation of pools in the splenic tissue. Some of these contained pinkish, granular material, probably laked blood, while others contained chiefly erythrocytes. The margins of the break in the splenic capsule showed no cellular reaction.

The lungs presented marked dilatation of the capillaries with erythrocytes and occasionally macrophages. In the sections of the right lower lobe there were focal hemorrhages.

The liver showed marked dilatation of the central veins and sinusoids. In some of the latter there were no recognizable red cells but only a granular fluid like that described in pools in the spleen. The cells of the liver cords were markedly granular with vacuolization of their cytoplasm.

The kidneys showed swelling of the cells of the convoluted tubules as well as pronounced granularity of their cytoplasm.

The uterus presented ulceration of the endometrium with a moderate polymorphonuclear infiltration of the surface. The blood sinuses were large and collapsed. The muscle fibers were hypertrophied.

Sections of the bone marrow revealed no abnormality. The heart, aorta, arteries, suprarenals, pancreas, breast, ovary, and gall bladder appeared normal.

#### DISCUSSION

In all, 22 cases including the present report, have been recorded in the literature. In addition, 6 cases of rupture of an aneurysm of the splenic artery complicating pregnancy were found (Smith, Wessenberg, Lundwall, Mayer, Remmelt,<sup>2</sup> and Bohler<sup>13</sup>). All the cases of splenic rupture occurred in white women, and these, with the exception of one, were multiparas. Due to a lack of sufficient information, the exact time in gestation at which this accident occurred was not definitely known in the entire group. Twenty of these cases give some information as to the time of occurrence in pregnancy. Of these, 12 occurred after viability, 7 early in pregnancy, and 1 in the immediate puerperium. Of the cases which happened late in pregnancy 5 occurred during labor, besides the present case (Kotschnew, Simpson, McMerrimey, Sommer and v. Hoch). In the last three cases mentioned, signs referable to subcapsular rupture of the spleen were present days before the actual onset of labor. Ten cases out of 22 came to surgery. Of these 8 recovered after splenectomy. One case (Smith, McMerrimey and Sladder) went on to term after having a splenectomy at three months.

Of the entire series 14 patients died. The cause of death of the majority of these was discovered only at post mortem. The difficulty of diagnosis, especially so in the presence of the gravid uterus, and the rapidity of death following this accident are responsible for the high mortality rate. Early in pregnancy the diagnosis is most often confused with ruptured ectopic gestation, later with premature separation of the placenta and rupture of the uterus. As pregnancy nears term the difficulty is manifoldly increased, and when rupture occurs during labor, as exemplified by this present case report, the diagnosis is almost an impossibility.

#### SUMMARY

1. A case of spontaneous rupture of the spleen complicating labor is reported. It is believed to be the first case recorded in the American literature.

2. Twenty-one cases of splenic rupture complicating pregnancy, labor, and the puerperium have been collected from the literature.

3. Due to difficulty in diagnosis and rapidity of death, spontaneous splenic rupture complicating labor may be an unrecognized cause, albeit a minor one, of fatal obstetric shock.

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## DIFFICULT LABOR DUE TO AMORPHOUS MONSTER

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**A**CARDIACUS AMORPHUS is a form of essential monster born with a separate homologous twin or triplet, which is usually normal and on which it depends for its imperfect development in the uterus. Only 8 cases of amorphous monster have been reported in the American literature since 1882.<sup>1</sup> Most of the reports have appeared in the German literature. We have been prompted to report this case because of its rarity and the difficulty it presented in delivery.

## CASE REPORT

Mrs. M. P., aged 37 years, gravida ii, had her last menstrual period on Dec. 7, 1938. Quickening was felt April 21, 1939 and her estimated confinement was Sept. 19, 1939. Her family history was negative. Four sisters and one brother were living and well. There was no history of multiple births, or the birth of monsters in her family to the best of her knowledge. Her past history was negative. Her menses began at the age of fifteen, occurring every twenty-eight days, and lasting five days with moderate flow and slight pain. She had been married four years. Her husband's health was good, and they had one child aged 2.5 years. Her previous delivery was normal and she had had no miscarriages.

The patient received routine prenatal care. Her abdomen seemed large during pregnancy but a multiple pregnancy was not diagnosed. Only one fetal heart was heard. No extra fetal mass was palpable in the abdomen. Prior to the delivery the uterus measured about six inches above the umbilicus.

The patient was admitted to the Barnert Hospital, Sept. 13, 1939, at 1:30 A.M. Her pains were irregular and by 9:00 A.M. were recurring regularly with moderate severity. At 1:20 P.M. she was delivered of a live female infant weighing 4½ pounds which presented by the breech but was delivered without difficulty. Following the birth of the baby, a mass was palpable in the abdomen, delivery of which was awaited about an hour. When this failed to occur, one ampoule of pituitrin was divided into three doses and each part was given at ten-minute intervals without effect. The patient was anesthetized and an intrauterine examination was made. A smooth rounded mass was felt which had an opening suggesting a mouth. This was grasped and delivery was attempted but was unsuccessful. Delivery was finally accomplished by making lateral incisions into the mass and placing the hooked ends of an obstetric forceps into each side. The monster was extracted in this way. A single placenta followed.

A normal amount of bleeding followed, and there were no lacerations. The mother was given sulfanilamide for a few days and recovery was uneventful. The baby was weak, nursed poorly, had facial twitching and nystagmus but left the hospital in fairly good condition on Sept. 24, 1939.



The amorphous monster was ovular in shape, measured 5.5 by 8 inches and weighed 1¼ pounds. At the cephalic end there was a thin tuft of hair. The skin was pinkish in color but appeared thicker than normal. The consistency of the mass was that of a soft fibroid.

*Pathologic Report.*—(Dr. Henry Brodie, Beth Israel Hospital, New York, New York.) *Gross Examination:* The specimen which was previously fixed and partly dissected was a flat ovoid mass whose (present) dimensions were 21 by 14 by 4 cm. There were no external appendages. There was no external distinction between head, thorax, and trunk. A segment of umbilical cord 9 cm. long was attached to an umbilicated area at one edge. The entire surface of the specimen, except for a previously bisected orifice on one flat surface, was covered with skin. Brownish black hair covered less than one-third of the specimen (Fig. 1). Within the orifice were several bonelike protuberances (probably maxillae) which on incision revealed a number of nonerupted teeth. When the skin in the region of the orifice was reflected, a mandible-like bone was found, underneath which was a tonguelike structure. Behind this was a cavity covered with a smooth membrane over which hung a uvulalike structure. To either side were cartilaginous structures suggesting turbinate processes. The pharynxlike cavity seemingly ended blindly. No esophagus was recognized.



Fig. 1.—Partly dissected ovoid mass without external appendages and covered with hair at the cephalic end.

About 5 cm. below the base of the tongue a branching set of small vessels led from a second cavity surrounded posteriorly and laterally by a bony cage which was formed by an incomplete vertebral column and a number of incomplete ribs. At the inferior edge of this cavity just to the right of the midline a purplish brown structure was found 1 cm. in diameter. On section this showed the characteristic markings of suprarenal tissue. To the left of the midline was a slightly smaller similar suprarenal. Below this was a piece of enteric canal blind at both ends. At its upper end immediately adjacent to the suprarenals was a firm nodule about 6 mm. in diameter which on section suggested pancreatic tissue. The piece of enteric canal, 4.5 cm. long and 6 mm. in average diameter, had a portion of short mesentery. The only other thoracic or infrathoracic organs recognizable were three tiny yellowish gray structures, the largest of which was about 3 mm. in diameter, and all situated close to the midline.

In the umbilical cord were two blood vessels, one thick and the other thin walled. The thin-walled vessel divided after passing within the umbilicated area.

One branch, together with the thick-walled vessel, passed superiorly in the direction of the suprarenals, passing dorsal to them. The vessels then subdivided to form the many branches mentioned above. No trace of a heart was found. The second branch was almost immediately lost in a mass of fat and connective tissue in the region of the umbilicus.

The specimen had previously been incised posteriorly in the cranial region. There was revealed a shell-like skull containing a remarkably well-formed brain in which cerebral hemispheres, cerebellum, and brain stem could all be recognized. There was a tremendous dilatation of the ventricular system. A short portion of vertebral column (5 cm. long) and in its spinal canal a spinal cord, 3 cm. long, were found. A depression was found in one of the flat bones in which was some soft tissue, part of which was black and suggested retina. This last named structure lay immediately behind the external orifice. No bilaterally symmetrical structure was found. No trace of either pectoral or pelvic girdle was seen, nor any appendicular skeleton.

*Microscopic Examination:* Sections from the enteric canal showed tissues similar to that seen in various portions of the normal gastrointestinal tract. In one section there was an area of bronchial epithelium with underlying mucinous glands and cartilage. The tongue showed a normal histologic picture with a small island of aberrant cartilage. The pancreas was well formed with acinar duct and island tissue.

The suprarenals were well formed. One of the tiny nodules was also suprarenal tissue. The other two nodules were ovary with numerous primordial follicles. No pituitary tissue was found in numbers of sections taken from the cranial cavity. One piece proved to be ganglion tissue, presumably Gasserian ganglion.

*Diagnosis:* Female acardiacus amorphus with incomplete formation of the central nervous system, cranial and axial skeletons, and an incomplete enteric canal with its derivatives.

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Kreis discusses the three types of menstrual disturbances which may arise during adolescence, namely, polymenorrhea, intercylic hemorrhage, and glandular hyperplasia. The diagnosis can only be made by curettement. The prognosis in polymenorrhea and intercylic bleeding is more favorable than it is for glandular hyperplasia. Treatment consists of the use of hemostatics, curettement, physical agents, blood transfusions and hormones, such as estrin, progestin, insulin, gonadotropic extracts and transfusions of blood from pregnant women.

Since recurrences are frequent, especially in the cases of glandular hyperplasia, regular treatment must be instituted. The author believes that in most of these cases the etiology is more constitutional than endocrine.

The frequency of syphilis, particularly hereditary syphilis and the therapeutic success obtained with specific treatment in these cases merits attention.

Operative interference is justified only when all other forms of therapy have failed. Repeated curettements should first be done, and if these are not curative, hysterectomy is the treatment of choice. The author warns against partial, temporary, or permanent castration.

J. P. GREENHILL.

# A MECHANICAL INK WRITING RECORDER SUITABLE FOR RECORDING UTERINE MOTILITY DURING PREGNANCY AND LABOR\*

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WHILE making capaeigraphic recordings of uterine activity during pregnancy and labor, it was recognized that the displacement amplitude was adequate to drive a simple mechanical lever system provided with an ink writer. No effort is made to record intrauterine tensions per se; specific efforts are made to record

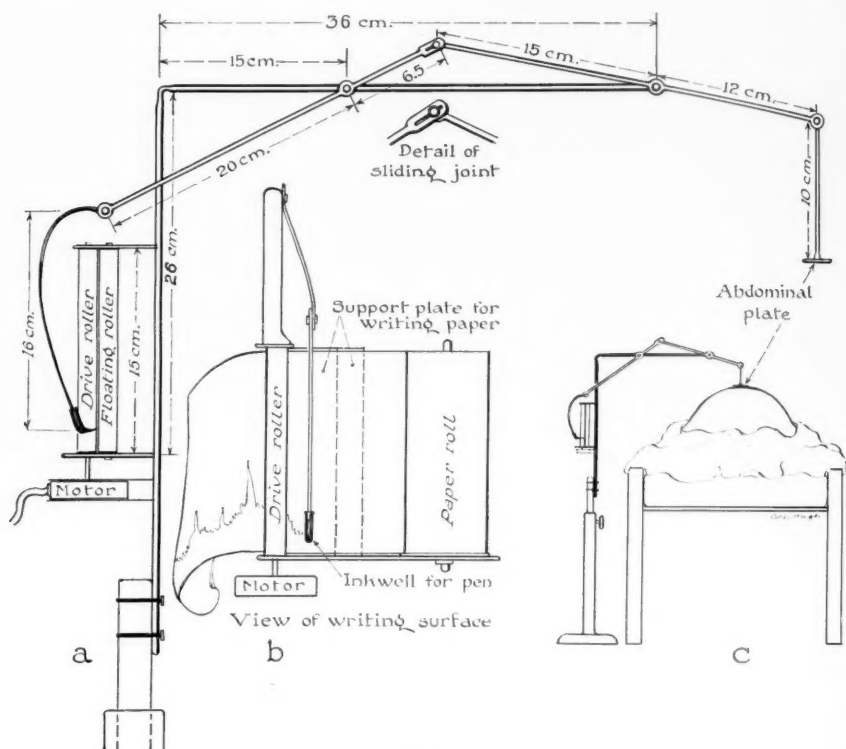


Fig. 1.

displacements, hence the use of a light lever system having an implication of four to one. Displacements associated with minor intrauterine tension changes and displacements localized in nature and not necessarily associated with intrauterine tension can be readily recorded.

The lever system is constructed of aluminum; the total weight resting upon the abdominal wall is 15 Gm. An increment of  $\frac{1}{2}$  Gm. is sufficient to overcome the bearing and writing point resistance. Theoretically, with proper materials and workmanship, the total weight upon the abdomen and the force necessary to overcome

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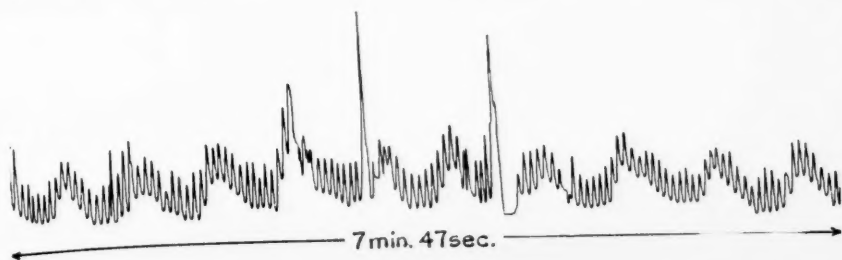


Fig. 2A.

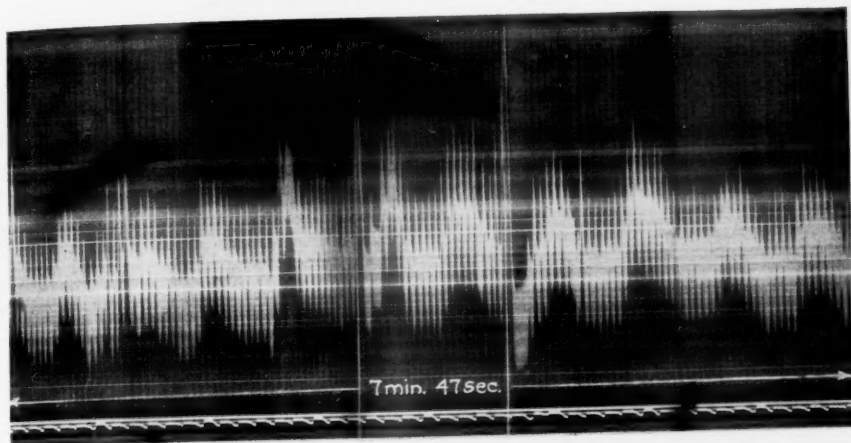


Fig. 2B.

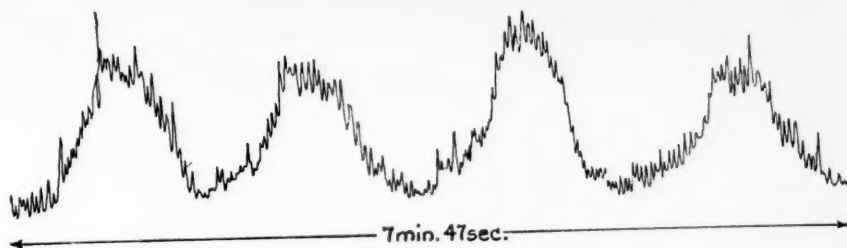


Fig. 3.

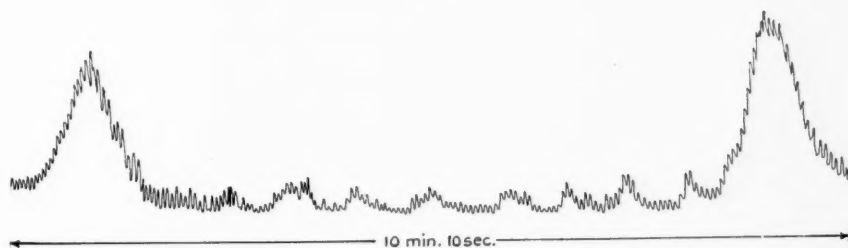


Fig. 4.

friction can be made negligible. However, an earlier model exerting 60 Gm. and having a relative high writer and bearing friction provided surprisingly good records.

A schematic view of the instrument in use is shown in Fig. 1, *c*. The assembly and measurements of the lever system are shown in *a* of Fig. 1. *b* of Fig. 1 shows the accessory equipment needed to drive the paper at a uniform rate.

Fig. 2*A* shows a typical recording obtained with the equipment. For comparison a simultaneous capacigraphic recording is also shown, Fig. 2*B*. The motility recorded is the most difficult type to record because of its low amplitude. In general, the two recordings are similar; maternal respiration, on occasion, when not masked, the maternal pulse, fetal activity, and uterine displacements are readily recognized. Minor differences, however, may be expected due to the fact that the capacigraph records the over-all abdominal displacement, whereas the mechanical approach records a point displacement.

Fig. 3 shows typical uterine displacements ordinarily recorded during early labor. Fig. 4 shows a recording in which there is rhythmic recurrence of two separate types of uterine motility in the pregnant uterus. Previous attention was called to this phenomenon.<sup>1</sup>

#### SUMMARY

A simple ink writing lever system suitable for recording uterine activity during pregnancy and labor is described and actual specifications supplied. The recorder provides records which fundamentally are the equivalent of capacigraphic recordings.

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## A TECHNIQUE FOR THE RECTAL ADMINISTRATION OF PARALDEHYDE

### PRELIMINARY REPORT

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PARALDEHYDE is generally conceded to be one of the safest of all the analgesic agents used in obstetrics. The analgesic and amnesic effects derived from adequate dosage are excellent. The one great disadvantage has been the difficulty of administration. Numerous methods have been devised to overcome this difficulty, but none have proved entirely satisfactory.

Paraldehyde was originally suggested in obstetrics by Davidoff and Rosenfeld,<sup>1</sup> who administered the drug by rectum in a small amount of olive oil. Colvin and Bartholomew<sup>2</sup> published their report shortly after and they used the same method of administration. They have since changed to the oral method.

Kane and Roth<sup>3</sup> added benzyl alcohol, a mild anesthetic agent, to the mixture. The results were rather disappointing, at least in our hands, and benzyl alcohol is a rather toxic drug. Dr. Kane is now using a mixture of paraldehyde and port wine administered by mouth for the initial dose.

Douglas and Peyton<sup>4</sup> advocated the administration of paraldehyde by mouth mixed with equal parts of aromatic elixir and chilled in cracked ice. They claimed that the action was more rapid, but admitted that vomiting frequently occurred.

DeCosta and Reese<sup>5</sup> tried to overcome the nauseous taste and odor of the drug by administering it in gelatin capsules by mouth. The number and size of the capsules necessary to administer a sufficient dosage makes this method objectionable to some patients. Furthermore, when the capsules dissolved in the stomach, a burning sensation, followed by vomiting, frequently resulted.

All of the oral methods have the disadvantage of being obnoxious to smell and taste and of causing gastric irritation, which results in vomiting in a large percentage of cases.



All of the rectal methods of administration have the disadvantage of causing a severe burning, and frequently an uncontrollable desire to expel the medication.

In order to overcome this effect, we have devised a method of administration which we feel is distinctly superior to any yet advocated. Our routine is as follows:

1. Soda bicarbonate enemas until returns are clear.
2. Morphine sulfate gr.  $\frac{1}{6}$  (hypodermic) and 5 c.c. of 1:1000 solution of nupercaine instilled into the rectum with an ordinary bulb syringe.
3. Nupercaine ointment smeared around the anus.
4. Ten to fifteen minutes later, paraldehyde drachms vi-viii, preceded and followed by drachm 1 of mineral oil or olive oil.
5. Paraldehyde, drachms iii-iv whenever the patient begins to arouse with her pains.

#### COMMENT

Nupercaine (Alpha-Butyl-Oxycinchoninic acid diethyl-ethylene-diamide hydrochloride) is a relatively nontoxic, rapid acting, topical anesthetic which produces an intense and prolonged local anesthesia. It does not irritate the rectal mucosa, or cause any impulse to defecate. It is much less toxic than cocaine, and much less expensive than some of the equally effective drugs such as butyn or metycaine. By administering it ten to fifteen minutes before the paraldehyde, we give it ample time to completely anesthetize the mucosa of the lower rectum. By anointing the anus with nupercaine ointment, we avoid the burning caused by the drops of paraldehyde remaining in the tube as it is withdrawn.

The administration of morphine ten to fifteen minutes before the paraldehyde, allows time for absorption of the drug. Morphine lessens peristalsis and relaxes the smooth muscle of the gut, thus inhibiting defecation. At the same time, the burning sensation is lessened by the analgesic effect of the morphine.

The chance for error is much lessened by this method, because each ingredient is administered separately, and may be checked immediately before its introduction.

#### RESULTS

This method has been used in 30 cases. In 21 cases, the results were excellent, none of these patients complaining of either burning or the desire to defecate. All of the remaining 9 patients had an impulse to expel the drug, and 4 of these had a burning sensation. One of these, a primipara with the head low, 5 cm. dilated, and having rather severe pains every three minutes, expelled the initial dose.

The duration of the unpleasant symptoms was much less than is usually seen with similar doses of paraldehyde by rectum, nor were the symptoms nearly so severe.

The best results were obtained in patients in early labor, where the need for immediate analgesia is not urgent, and the pains are not expulsive in character. In the latter part of the first stage, or in the second stage, better results are obtained by giving the dose of paraldehyde while the patient is under light ethylene anesthesia. The ethylene is continued for ten to fifteen minutes after the administration to allow the paraldehyde to become partially absorbed.

#### SUMMARY

We present here a new technique for the rectal administration of paraldehyde. The method is safe, inexpensive, and effective in relieving the burning sensation, and the desire to expel the medication, which usually accompanies the rectal administration of the drug.

The technique has been used in 30 cases, with excellent results in 21, nine desired to expel the medication, and 4 had some burning. One patient expelled her initial dose.

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## TATTOOING (PUNCTURATION) WITH MERCURY SULFIDE FOR THE TREATMENT OF INTRACTABLE PRURITUS CAUSED BY LEUCOPLAKIA-KRAUROSIS VULVAE

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TATTOOING with mercury sulfide has been successfully employed for the treatment of pruritus ani,<sup>1, 2</sup> and for pruritus perinei caused by an extension of the perianal itching.<sup>3</sup> Because of the similarity in the histologic appearance of pruritus vulvae and pruritus ani,<sup>4</sup> it was decided to investigate the value of this procedure in the treatment of the former condition.

This report concerns the successful employment of tattooing with mercury sulfide for the treatment of intractable pruritus caused by leucoplakia-kraurosis, which had not been controlled previously by partial vulvectomy and four additional surgical procedures.

### CASE REPORT

L. S., a 32-year-old white woman, gravida and para iii, was admitted to the hospital Jan. 15, 1936, because of intense pruritus vulvae and ani. The menstrual periods were regular and normal. She had been seen in the Out-Patient Department Jan. 6, 1934, because of constipation, pain on defecation, and pruritus ani. At that time rectal examination revealed tenderness on digital exploration as well as perianal and perineal fissures. Late in 1935 there was observed an atrophic vaginitis with maceration of the labia, which had failed to respond to conservative treatment. Physical examination on this admission was normal except for atrophy with fissuring and maceration of the tissues involving the clitoris, the upper margin of the urethra, the labia minora, the fourchette, and the perineum. In view of the fact that the intense pruritus was not relieved by estrogenic therapy and hygienic measures, a partial vulvectomy was performed without removing the perineal skin. Histologic examination of the excised tissue showed hyperkeratosis, chronic inflammation, and disappearance of elastic fibers. This histologic appearance was regarded as compatible with the diagnosis of leucoplakia and kraurosis.

The patient was readmitted to the hospital May 15, 1936, because of pruritus ani and perinei of increasing severity. On examination there was no change in the pathologic process of the perineum; there was no evidence of recurrence at the site of vulvectomy. The perineal skin and subcutaneous tissue were removed three days later. The histologic examination of the excised tissue showed leucoplakia and chronic inflammation.

Mild pruritus in the perineal and perianal region continued. In February, 1937, there was observed a recurrence of the original pathologic process in the perineum, accompanied by a fissure extending to the anal orifice. Five weeks later, the patient was readmitted to hospital where the lesion in the perineum was removed. Examination of the excised tissue revealed histologic changes consistent with the diagnosis of leucoplakia and chronic inflammation.

The patient remained well for about two months, and was again admitted to hospital Jan. 26, 1938, because of pruritus and a burning sensation more intense on the left side of the introitus. Examination revealed a thickened and a yellowish white area with deep fissures in the perineum, and atrophy along the left side of the introitus, extending to the anal region. The vagina admitted two fingers, was soft, and resilient. At this time the involved tissues of the left side of the introitus and of the perineum were removed. The histologic examination of the excised tissue showed leucoplakia and kraurosis.

The patient remained well until June, 1938 (a period of four months), when she experienced a recurrence of the itching and burning in the introitus, the intensity of which was increased during the menses. Examination showed a normal uterus and

adnexa. There was atrophy of the skin adjacent to the clitoris and recurrence of the kraurotic-like process at the vaginoperineal junction. As a result of the previous operative procedures the posterior vaginal mucosa had extended over the upper one-third of the perineum. At its distal portion, it was partially epithelialized and atrophic. In the intergluteal region there was a bilateral, symmetrical area of parchment-like atrophic skin which extended to and encircled the anus. On October 19, 1938, the atrophic skin of the subclitoric region, and the kraurotic-like process at the vaginoperineal junction were excised. Fragments of the excised skin showed areas of chronic nonspecific inflammation without evidence of kraurosis. November 10, several Thiersch grafts were implanted upon the granulating perineal area.

There was continuous itching and soreness in the region about the left side of the introitus and over the entire perianal area. Re-examination June 5, 1939, showed a narrowing of the introitus and a whitish plaque about the anterior commissure. The skin of the posterior commissure, the terminal inch of the mucosa of the vagina, and the skin of the perineum extending to and surrounding the anal orifice had changed to a white, thick, cornified plaque. The perianal skin was tense, shiny white in appearance, and parchment-like in consistency. The crural folds presented the same appearance and were also fissured.

Physical examination was otherwise normal; there was no evidence of disease of the nervous system to account for the local manifestations. The essential laboratory tests were negative. The dermatologist (Dr. L. Chargin) agreed that tattooing with mercury sulfide should be given a trial.

On June 7, 1939, the perianal and the perineal regions were tattooed with mercury sulfide under infiltration anesthesia, using 1 per cent solution of procaine hydrochloride, according to the technique described in another communication.<sup>2</sup> Seven days later, the vulva was similarly tattooed with mercury sulfide under avertin supplemented by infiltration anesthesia. One month later, the skin about the introitus and in the perianal region, with the exception of the perineal area, was normal in appearance. At the time of writing (a period of over nine months), the patient has remained free of pruritus in spite of the presence of moderate excoriation of the perineum. The latter is believed to be caused by a continuous escape of vaginal discharge which has not been treated because the patient prefers to leave "things well enough alone."

#### DISCUSSION

The results obtained in this patient seem to indicate that tattooing with mercury sulfide is advisable for the treatment of this type of lesion in selected cases. It is still unexplained how mercury sulfide deposited in the corium by tattoo acts in relieving localized pruritus.<sup>3</sup> Control studies have shown that mechanical trauma alone as produced by the tattooing machine without the use of mercury sulfide is ineffectual in controlling pruritus and permanently.<sup>2</sup> It is likely that the intracutaneous deposit of mercury sulfide produces a degenerative effect on the cutaneous terminal nerve endings and twigs, altering their capacity to respond to normal stimuli. Study of the changes in the cutaneous sensory modalities thus produced is in progress.<sup>5</sup>

It is believed that the alteration in the cutaneous modalities is proportional, within limits, to the amount of the intracutaneous deposit of mercury sulfide. This belief is rendered more likely by the following observation: In an instance of pruritus ani,<sup>3</sup> unilateral recurrence of pruritus was noted in the particular area where a smaller intracutaneous deposit of mercury sulfide was made as indicated by a lighter red color on that side. A study of the status of the cutaneous sensory modalities disclosed that the opposite perianal area which was adequately tattooed and free from pruritus had fewer nerve endings capable of responding to tactile and painful sensations.

#### SUMMARY

A patient with intractable pruritus caused by leucoplakia-kraurosis was successfully treated with the intracutaneous deposit of mercury sulfide by tattoo, after a partial vulvectomy and four subsequent surgical procedures for the removal of involved or recurrent areas of skin had failed to control the distressing pruritus.

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876 PARK AVENUE

### A NEW SCISSORS FOR INCISING THE UTERUS IN CESAREAN SECTION\*

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IN performing cesarean section, most operators open the uterus by making a small incision with a scalpel and completing it with a bandage scissors. This type of scissors is used to protect the fetus from injury by the edge of a scalpel or by the points of an ordinary scissors.

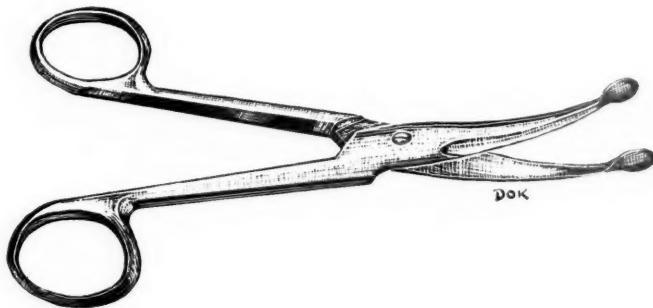


Fig. 1.

The past two years have seen a rapid rise in popularity of the transverse uterine incision. Here, it is important to curve the ends of the incision upward, to avoid the uterine arteries. To make this "U" incision more easily, some surgeons employ a "curved on the flat" Mayo scissors.

We have devised a scissors which utilizes the important features of both these instruments. Its blunt points and "side-ways" curve, make it the ideal instrument for transverse uterine incisions.

50 EAST 78TH STREET

\*This instrument is manufactured by N. S. Low & Co., Inc., New York City.

## BRENNER TUMOR OF THE OVARY COMPLICATING LABOR

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THIS case of Brenner tumor of the ovary blocking the pelvis and preventing normal delivery is reported because it is a rare tumor, complicating pregnancy and producing dystocia. Novak and Jones report three cases of Brenner tumors complicating pregnancy in which one patient was operated upon when she was four months pregnant; another in which the diagnosis of pregnancy was made only by the finding of decidual tissue after curettage; and a third case in which the patient had six previous pregnancies, five terminating in abortions, and one in a premature stillbirth at the seventh month. It is interesting, therefore, to record this case as complicating a full-term pregnancy.

The patient, a 27-year-old primigravida, was admitted to the Franklin Square Hospital on Jan. 17, 1940. External pelvic measurements were all normal. Last menstrual period occurred on April 13, 1939 and the expected date of confinement was Jan. 20, 1940. Prenatal course was essentially normal until one week prior to hospitalization, when the patient developed an elevation of blood pressure for which she was treated at home by diet, rest, and catharsis. On the day of admission to the hospital the patient's blood pressure at home was said to be 190/110 and she complained of headaches and vomiting.

On admission her blood pressure was 150/100; urine showed a trace of albumin; duration of pregnancy was at term. Fetal heart was heard in the lower left quadrant, presenting part was at the superior strait. There was no edema of the face nor of the lower extremities, and rectal examination showed the cervix to be completely effaced, and canal closed; head not engaged. Blood chemistry: nonprotein nitrogen, 30.6 mg.; uric acid, 2.8 mg.; creatinine, 1.5 mg.; sugar, 102 mg.; Wassermann, negative; Hg, 85 per cent.

The patient was treated conservatively. She was put on a low protein, salt poor diet, and fluids forced to 3000 c.c., including carbohydrate drinks. She was given  $\frac{1}{4}$  gr. of morphine at once and 1 gr. of luminal four times daily. One ounce of magnesium sulfate every morning. The blood pressure readings were taken every three hours. Under this treatment her systolic blood pressure had a tendency to fall, but the diastolic remained rather stationary, around 100. Blood pressure was stabilized at 140/100. Urine subsequently showed no albumin, headaches disappeared, and the patient appeared comfortable. After three days of conservative treatment, since the patient was at term and her blood pressure was remaining stationary, medical induction of labor was instituted by the use of castor oil, quinine, and hot enema, but was ineffectual. On the following day medical induction was continued by the use of pitocin, 2 min. every half hour for three doses. This, likewise, was unsuccessful. On January 23, induction of labor by rupturing the membranes was considered. At this time it was found that there was a mass lying in the pelvis below the promontory of the sacrum about 5 by 4 inches, which felt rather doughy and could not be pushed out of the pelvis. The cervix was above this mass, the canal was completely effaced, and the os about 2 to 3 cm. dilated. The head was not engaged. On rectal examination this mass was found to lie outside the rectum. A diagnosis of ovarian tumor or fibroid, blocking the pelvis, was made.

The following day a low cervical cesarean section was performed, and the patient delivered a living female child, weighing 7 pounds 4 ounces. The baby was found lying in left sacroanterior position and slightly transverse. Following the completion of the closure of the low uterine segment, the left ovary was examined and found to be normal. The tumor lying in the pelvis was easily removed and found to be a solid tumor of the right ovary rather larger than was estimated at the time of pelvic examination, and had a long pedicle; in addition to this, on



the fimbriated end of the right tube was a cyst of Morgagni. The ovarian tumor was removed, as well as the cyst of Morgagni. The abdomen was closed in the usual manner, and the mother left the operating room in good condition.

Puerperium was essentially normal, except for a postoperative rise of temperature on the first and second days to 102°F., and the pulse was 120, which returned to normal on the third day and remained so throughout her stay in the hospital. Abdominal wound healed by primary intention, and mother was discharged on February 7, fifteen days postoperatively, in good condition. Her blood pressure had returned to normal and at the time of discharge was 130/80. Urinalysis at discharge was negative.

2309 EUTAW PLACE

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### THE PREVENTION OF POSTOPERATIVE TRAUMATIC AND CATHETER CYSTITIS

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(From St. Mary's Hospital)

THIS problem has occupied our attention for many years, and after trial of numerous methods with varied success, we have finally come to the conclusion that the one herein described has given us almost uniformly good results with a minimum of discomfort to the patient, and with the least number of unpleasant sequelae.

We have felt all along that we confer a doubtful benefit if, in curing a patient's pelvic pathology or repairing her hernia of pelvic organs, we leave her with a residual cystitis, or, worse still, with a uni- or bilateral pyelitis.

These are the common complications of extensive repair operations and, in spite of all our previous study in this important matter, these sequelae were all too common. The great majority of repair cases come to operation in the later years of their life. Their pelvic tissues are postmenopausal in their atrophy and lowered in their healing power. Consequently, any postoperative inflammation in the nature of cystitis is often hard, sometimes impossible, to cure.

Pyelitis following repair operations upon the anterior vaginal wall is also an all-too-common postoperative complication. The cause of this is not hard to find. If one examines the interior of the bladder after an extensive radical cure of cystocele, the bladder mucosa is thrown into folds due to the plication of the redundant mucosal lining of the bladder, which has stretched to keep pace with the progressive descent. As a consequence the circulation of the bladder is interfered with, and local edema often occurs. Catheterization, therefore, even when carried out with meticulous aseptic care, may result in implanting an infection upon these adult, atrophic, strangulated tissues. Moreover, postoperative catheterization of the ureters in extensive repair cases frequently demonstrates a kinking of the vesical ends of the ureters, owing to suturing the cardinal ligaments in front of the cervix, and a consequent great or small amount of ureteral urinary retention, with consequent frequency of pyelitis. Our study shows that in the vast majority of cases of postoperative urinary retention there is a nervous or traumatic inhibition of bladder function and, frequently, a degree of obstructive ureteral flow. To overcome this in great part, if not wholly, it is advised to keep the patient in bed during the period of preoperative care and study of the case, when the blood, blood sugar, and other tests are being carried out. Do not allow her bathroom privileges, so that she becomes inured to the use of the bedpan for evacuations before the added inhibition of the operation. We have found that the number of cases of urinary retention is inversely as the length of time that the patient is thus educated. At the time of operation, when any extensive operation is performed upon the anterior vaginal wall, and thereby the foundations of the bladder are disturbed, a slashed Malecot

catheter dipped in liquid paraffin is inserted into the bladder and the outer end of the catheter is clamped with an artery forceps (Fig. 1) or screw clamp, and the latter is pinned to the abdominal binder so as to allow considerable slack in the catheter. In this manner, the patient can move about in bed without discomfort. The forceps is released every three hours and the urine drawn off. This alternate emptying and filling of the bladder allows the intravesical portion of the catheter to move, and prevents the constant impinging of this portion upon a fixed spot of the trigone, as happens when continuous drainage over the side of the bed is employed. Continuous drainage is used only in cases where damage to the *continuity* of the vesical mucosa is known or suspected. Moreover, by this method, the alternate emptying and filling of the bladder helps to overcome any muscular paresis which may have resulted from nerve trauma. The patient is then given 4 tablets of 5 gr. each



Fig. 1.—Catheter and screw clamp in situ. Fixation to binder by means of safety pin.

of neoprontosil daily. Some patients cannot swallow these. Then they may chew them, which colors the mouth and lips a bright red. In cases of emesis or intolerance of the drug, owing to gastric upset, the aseptic solution of neoprontosil may be used intramuscularly in doses of 10 c.c. twice daily. The urine soon takes on a distinct orange color, and we have noted uniform freedom from purulent infection. The catheter is left in situ from three to five days. Twenty-four hours before removing it, the patient is given 3 doses of thiamin chloride, each of 1,660 international units, subcutaneously or intramuscularly, to stimulate involuntary muscle activity. The action of vitamin B<sub>1</sub> upon an involuntary muscle of the various viscera is well known.

It is rare that retention follows this procedure and the results of this treatment, as regards both the incidence of postoperative cystitis and pyelitis even in the oldest of patients, have been uniformly gratifying, and recoveries have been consequently much smoother and free from the immediate discomforts of frequency and pain, and equally, from the remote consequences of pyelitis and cystitis.

1472 SHERBROOKE STREET

## Special Article

### "ANESTHÉSIE À LA REINE"

#### A CHAPTER IN THE HISTORY OF ANESTHESIA

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QUEEN VICTORIA was delivered of Prince Leopold, her eighth child, on April 7, 1853. She was attended in confinement by Sir James Clark, Bart. M.D., and John Snow, M.D. The latter was present in the capacity of anesthetist, and the event is historical in the annals of obstetrics because Her Majesty was the first crowned head to receive the benefits of anesthesia in childbirth. Chloroform was administered on a handkerchief in 15 minim doses, the inhalation lasting fifty-three minutes. The drug was administered intermittently and induced what we think of as "inhalation analgesia," for the patient was not unconscious at any time. The Queen expressed herself pleased with the effect. Her attendant, Sir James Clark, well appreciated the importance of the event and the effect that it would have in influencing the establishment of anesthesia in obstetrics, for shortly afterward he wrote to James Y. Simpson, "I know this information will please you, and I have little doubt it will lead to a more general use of chloroform in midwifery practice in this quarter than has hitherto prevailed." Today the event is memorialized in obstetric parlance by the phrase "*anesthésie à la reine*," which signifies the peculiar type of intermittent inhalation anesthesia which has become so useful in obstetric practice.

Other than the facts stated above not much was recorded of the details of the birth. We do know that Dr. Snow had previously been consulted on the occasion of the birth of Prince Arthur in 1850 but had not been called in to render service. We also know that previous to the birth of Prince Leopold he had had an interview with the consort, Prince Albert, and was much impressed with the kindness and intelligence which that gentleman showed concerning the scientific points which formed the subject of their conversation. Later, in 1857, the Queen was again to receive the ministrations of Dr. John Snow at the birth of Princess Beatrice.

Both James Clark and John Snow had interesting and notable careers, the latter being an important figure in the annals of anesthesia and epidemiology, and the former the most important physician in court circles in his day. When James Clark, in 1834, was appointed to the post of physician to the Duchess of Kent, the Queen's mother, something of a sensation was created for a biographer states that the Fellows of the exclusive College of Physicians, "looked on the appointment of a northern graduate much as the bench of bishops might resent the intrusion of a Dissenter." Clark was without question "northern" for he had been born in Banffshire, Scotland, and had been educated at Aberdeen and Edinburgh. From the latter institution he had been granted the M.D. degree in 1817. Two years later he went to Italy and settled in Rome. It is gratifying to learn that

while practicing here he devotedly attended John Keats during the poet's last illness. In 1826 Clark decided to remove to London and while on his way thence, at Carlsbad he had the fortune to meet Prince Leopold of Belgium. Here the Prince found the young physician much interested in the therapeutic uses of the waters, and on his return to London appointed him his physician. Later at his recommendation Clark was appointed the physician to his sister, the Duchess of Kent.

When the young Queen ascended the throne, the story is told that the Premier presented Her Majesty with a list of physicians, at the very bottom of which was James Clark. She is reported to have taken a pen and crossed out the name, rewriting it at the top of the list.

As physician to the Queen, James Clark had a notable and influential career, and it was said that, with Sir Benjamin Brodie, he was one of two men through whom the influence of the medical profession was chiefly exerted on the state. At one time, however, he became intensely unpopular, owing to his supposed conduct in the case of Lady Flora Hastings. The growth of a fatal abdominal tumor had led to the unjust suspicion that this unmarried court lady was pregnant. In reviewing the facts of the case it seems clear that if the advice and counsel of Sir James had been followed from the start a very troublesome episode might have been avoided. The fact that the lady would not allow an abdominal examination until some weeks had passed gave the scandal mongers time for their ghastly work, and both the doctor and the court were subjected to a degree of scurrility which may be somewhat judged by the amount of literature on the subject which was produced. It is gratifying to note that "long before his death almost everybody knew, more or less distinctly, that he had been wrongly blamed." In addition to the important influence which James Clark had on the affairs of state, he was recognized as an authority on climate in its relation to disease and published two works on the subject. In 1870, at the age of 81, Sir James Clark died.

The career of John Snow was singularly different from that of Clark. Born in York in 1813, his relatively short life of 45 years was filled with scientific achievement. His biography by Sir Benjamin Ward Richardson is entitled, "John Snow, M.D. A Representative of Medical Science and Art of the Victorian Era." His signal contributions to epidemiology can merely be mentioned here, but it is significant that in 1936 a reprint of two of his papers on cholera was published in book form by The Commonwealth Fund. In the introduction by Wade Hampton Frost, we find these words, "Some part of Snow's conception that cholera was due to a specific micro-organism, an obligate parasite, propagating only in the human intestinal tract and disseminated by the ingestion of excreta, was expressed by a number of contemporary writers; but seldom if ever was the whole idea expressed, and no one else followed it through to such full development."

Snow's interest in anesthesia had been somewhat prepared before its announcement in 1846. For some time he had been engaged in experiments on respiration and asphyxia, and five years before that event he had published a paper entitled "Asphyxia and on the Resuscitation of Newborn Children." The first ether anesthetics in England were not too successful but Snow brought the administration to perfection by the invention of an inhaler. In a short time the lead-

ing surgeon in London, Liston, recognized his ability and as a result he became the leading anesthetist in that city. When chloroform was discovered he made extensive animal experiments with the new drug and gave up his predilection for ether. For ten years preceding his death he is said to have averaged 450 administrations yearly.

Snow's chief work on anesthesia was published shortly after his death in 1858. This work, *Chloroform and Other Anaesthetics*, shows his fine scientific mind and his wide experience in the subject. The chapters dealing with parturition are of definite interest to us for they show how well he understood this field. He writes, "The most usual time when the accoucheur and I have determined that the inhalation should be commenced, has been when the os uteri was nearly dilated to its full extent, and the pains were taking on an expulsive character. . . . In such cases when it has been determined to resort to inhalation the moment to begin is at the commencement of a pain; and the chloroform should be intermitted when the uterine contraction subsides, or sooner if the patient is relieved of her suffering." We find here also this fine description of the procedure which is the title of this paper. He writes:

"The effects of chloroform on the brain should not be carried during labour beyond what I denominate the second degree of narcotism, or that condition in which the mental functions are diminished, but not altogether suspended, except when the effect of the vapour is associated with natural sleep. The patient under the influence of chloroform to this extent, has no longer a correct consciousness of where she is, and what is occurring around her, but is capable of being aroused to give incoherent answers, if injudiciously questioned. In this state, the patient will sometimes assist the labour by bearing down voluntarily, if requested to do so, and be otherwise obedient to what is said; and by withholding the chloroform for a few minutes, she at any time becomes quite conscious. As a general rule, it is desirable not to hold any conversation whilst the patient is taking chloroform, in order that her mind may not be excited. The plan mentioned above, of giving the chloroform very gently at first, also has a tendency to prevent its causing mental excitement, the patient coming gradually under its effects. In surgical operations, excitement of the mind can nearly always be avoided by carrying the patient pretty rapidly into a state of insensibility, in which the mental functions are necessarily suspended. But in the practice of midwifery, it is not allowable to cause a state of coma or insensibility, except in certain cases of operative delivery, hereafter to be mentioned."

This author's scientific approach to the problems of anesthesia is evidenced by his many experiments with other gases. His attention was also drawn to local anesthesia and he performed experiments with freezing mixtures, including the use of solid carbonic acid as applied to the skin. His biographer Richardson describes him as, "of middle height, of somewhat slender build, and of sedate expression. His long life in comparative student loneliness had made him reserved in his manner to strangers. . . . He kept a record of all his experiments and short notes of observations made by his friends."

It may be interesting for us to consider some of the historical facts concerning anesthesia in obstetrics and in particular of intermittent anesthesia as applied to normal labor. The first application of inhalation anesthesia was that made by James Y. Simpson on Jan. 19, 1847, the details of which were published in *The Edinburgh Monthly Journal of Medical Science* in February of that year. The case was that of a lame woman, a gravida ii, who presented a badly distorted pelvis and whose first pregnancy had been ended by craniotomy after a four-



day labor. Under total anesthesia the second labor was completed by Simpson by a difficult version and extraction. The inhalation lasted twenty minutes.

In March of the same year Simpson published a paper, "On the Inhalation of Sulphuric Ether in the Practice of Midwifery." In a footnote he wrote, "I have during labor, kept patients under its influence for upwards of half an hour. In exhibiting it, the first or exhilarating stage of its effects should be passed through as rapidly as possible." Later in this year on the first of December Simpson read a paper at the Medico Chirurgical Society of Edinburgh on, "Superinduction of Anaesthesia in Natural and Morbid Parturition; with cases illustrative of the use and effects of Chloroform in Obstetric Practice." At that time he stated that since the latter part of January he had employed anesthesia with few exceptions in every case of labor which had been under his care and had kept up the anesthetic state from a few minutes to a number of hours. Under Case VI of this series we find a statement which seems illustrative of the procedure which he had adopted for normal labor. He writes, "She lay as usual like a person soundly asleep under it, and I was now able without any suffering on her part, to increase the intensity and force of each recurring pain, by exciting the uterus and abdominal muscles through pressure in the down part of the vagina and perineum." It seems quite evident in this case that voluntary efforts on the part of the patient were in abeyance and that unconsciousness was complete. That this method of procedure was Simpson's usual practice seems further borne out by his summary of cases in which he expresses himself, "the preceding instances, afford perhaps, a sufficient number of examples of the use of chloroform in natural labor. . . . The mothers instead of crying and suffering under the strong agonies and throes of labor have lain in a state of quiet placid slumber, made more or less deep at the will of the medical attendant, and, if disturbed at all, disturbed only unconsciously from time to time by the recurring uterine contractions producing some reflex or automatic movements on the part of the patient—like those of a person moving under any irritation of the surface, or from the touch of another, though still in the state of sleep."

Here again the inference is plain that consciousness was abolished by the anesthetic and that voluntary efforts on the patient's part were not used. This same concept is again seen in his paper of December, 1847, on the "Anaesthetic and Other Therapeutic Properties of Chloroform." He writes, "A few inhalations given then, and repeated with each recurring uterine contraction, keeps the patient in a state of unconsciousness; and this condition may be easily maintained for hours by administering in this way the chloroform vapor with each pain, and withdrawing it entirely during each interval." It is apparent that this method of anesthesia is essentially different from that described above by Snow and from that administered by him to the Queen, who "was not unconscious at any time."

From the evidence at the disposal of the author of this paper it seems quite clear that the first description of "anesthésie à la reine" is to be found in the account of the first case of anesthesia in labor which occurred in the United States. In the *Boston Medical and Surgical Journal* for April 14, 1847, the following letter from Dr. N. C. Keep is an important record.

"To the Editor of the Boston Medical and Surgical Journal.

"Dear Sir:

"On the seventh instant, I administered the vapor of ether in a case of natural labor. The patient was in good health, and in labor of her third child. Five and a half hours having elapsed from the commencement of labor, her pains, which had been light, but regular, becoming severe, the vapor of ether was inhaled by the nose, and exhaled by the mouth. The patient had no difficulty in taking the vapor in this manner from the reservoir, without any valvular apparatus.

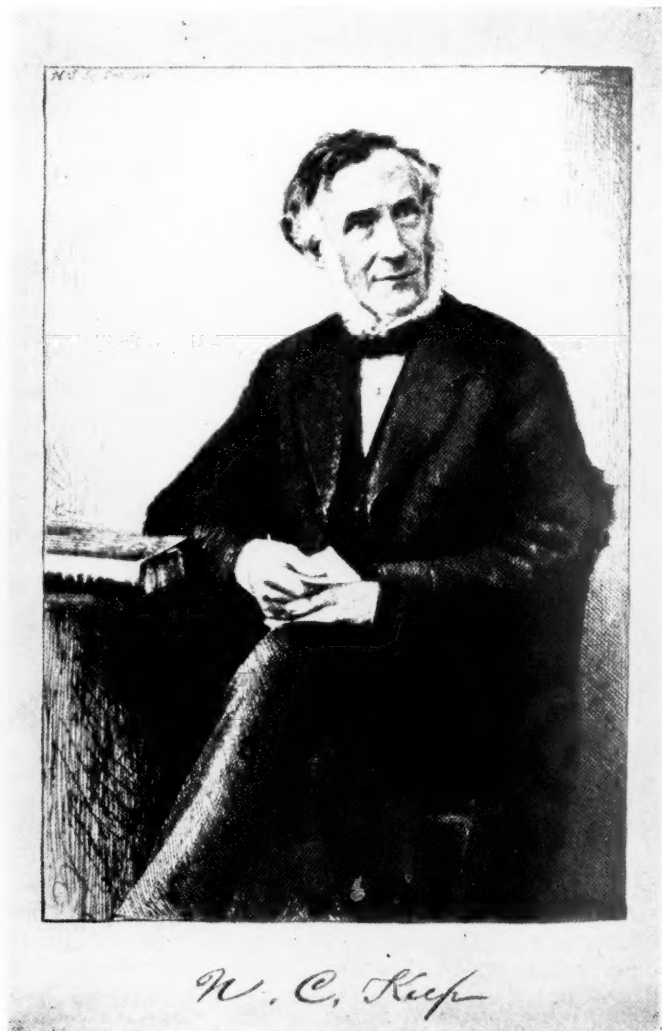


Fig. 1.—N. C. Keep. (Printed, by permission, from Hapgood: *History of the Harvard Dental School*.)

"In the course of twenty minutes, four pains had occurred without suffering; the vapor of ether being administered between each pain. Consciousness was unimpaired, and labor not retarded. Inhalation was then suspended, that a comparison might be made between the effective force of the throes with and without the vapor of ether. No material difference could be detected; but the distress of the patient was great. Inhalation was resumed; but the progress of the labor was so rapid, that

time could not be found for sufficient inhalation to bring the system perfectly under its influence: still the sufferings of the last moments were greatly mitigated. From the commencement of the inhalation to the close of the labor, thirty minutes. Number of inhalations, five. No unpleasant symptoms occurred and the result was highly satisfactory.

Yours &c

N. C. Keep"

"Boston, April 10, 1847.

This case which occurred less than three months after Simpson's first administration is clearly that in which inhalation analgesia was used. Walter Channing, America's champion of anesthesia in child-birth, sensed the importance of the observation and commented upon it as follows, "It is the first case in which sulphuric ether was exhibited by inhalation in labor in this country. Besides its historical interest, it has in itself much which is practically useful. Thus, ether was inhaled 'between each pain.' Consciousness was unimpaired, and labor not retarded."

The administration of ether as an anesthetic was not a novel experience for Dr. Keep, for he had for some time been using ether in the practice of dentistry, in which he was then engaged. In a previous communication he had written concerning its administration, "In the last 200 cases (nearly all intelligent persons, capable of accurate observation) I have not known one who was not conscious of existence, of time, and of the operation that was being performed, but though the intellect was nearly or quite undisturbed, the sensibility to pain has been uniformly greatly diminished, and generally entirely lost. . . . I have extracted teeth for persons of all ages, from 6 to 60. . . . I have destroyed the entire nerve of the tooth for a number of persons while under the influence of the vapor. . . . I entertain the opinion that the inhalation of the vapor of ether, when administered in a proper manner, by a person understanding it, and capable of regulating its quantity and power, as every person using it should be able to do, is safe, and will greatly mitigate, and in most cases take away all pain in dental and surgical operations." It is clear from this that the writer of this communication was using inhalation analgesia and explains very well his technique of administration in the case of labor which he reported. He was adapting to obstetric procedure a method with which he was thoroughly familiar, and that it was carefully planned is further witnessed by the deliberate suspension of anesthesia in order to study the effect on the force of the uterine contractions. This contribution to anesthesia in obstetrics was an important landmark in the history of that subject.

The career of Keep in the development of dental surgery in America was one of outstanding achievement. To him the Harvard Dental School owes its existence, for through his influence the school was established as an integral part of Harvard University, the first association of its kind in the United States. Nathan Cooley Keep was born at Longmeadow, Mass., on Dec. 23, 1800. He attended the village schools and at the age of 16 he was apprenticed to John Taylor, a manufacturing jeweler in Newark, New Jersey. He served an apprenticeship of five years during which time he became interested in dentistry. In 1821 he entered the Harvard Medical School and graduated in the class of 1827 with the degree of M.D. For the next forty years he

practiced dentistry in Boston, devoting himself particularly to mechanical dentistry, the forerunner of prosthesis. When the first faculty of the Harvard Dental School was appointed on Nov. 30, 1867, Nathan Cooley Keep, M.D., was elected Professor of Mechanical Dentistry, and on March 19, 1868, he was elected the first Dean of the Dental School Faculty. His career as a leader in the development of his profession is well known and does not need further elaboration here, but his part as a witness in one of the great murder trials of his day is of interest. It was upon his testimony that Professor Webster was convicted of the murder of his colleague, Professor Parkman. Soon after the murder, a set of false teeth was found supposed to have belonged to Parkman. Some years before Keep had made a set for Parkman and when the molds for this set were produced in the courtroom it proved the ultimate dramatic note in the trial which convicted Webster. After the murderer had killed his victim he burned the body in the furnace and the only remaining evidence which withstood the flames was the set of porcelain teeth.

As a recognition of his services to dentistry, Dr. Keep was awarded the honorary degree of D.M.D. by Harvard in 1870, and previously he had been honored by the honorary degree of D.D.S. by the Baltimore College of Dental Surgery in 1843. On March 11, 1875, seven years after the establishment of the Harvard Dental School, its founder and first Dean, Nathan Cooley Keep died.

Such in brief is the story of an obstetric expression, "anesthésie à la reine," a phrase which is found chiefly in textbooks and whose meaning is much better defined by the term *obstetric inhalation analgesia*. That the latter procedure is a definitely obstetric technique there is but little question, and when we consider its evolution it seems obvious that it should be a natural development in the application of anesthesia to obstetrics. That it was an early development was undoubtedly due to its use as a technique in dentistry by a man who was both a physician and a dentist and whose scientific mind led him to apply it at the first opportunity in an untried field. In the history of anesthesia, as applied to obstetrics, Nathan Cooley Keep was a real pioneer.

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# Department of Maternal Welfare

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## THE SMALL HOSPITAL AS AN OBSTETRIC HAZARD

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SUBSEQUENT to the recent publication of a study of obstetric results,<sup>1</sup> J. B. DeLee<sup>2</sup> was one of those who raised the question as to the number of general hospitals in the United States in which obstetrics was being practiced and in which the patient's protection was not adequate. It is in an attempt to make a partial answer to such questions that this study was undertaken.

The report of the committee of the American Hospital Association under the chairmanship of Dr. Buerki,<sup>3</sup> the report of the American College of Surgeons,<sup>4</sup> and the standards adopted by the Hospital Obstetric Society of Ohio,<sup>5</sup> have clearly defined the requirements that should be met by any general hospital undertaking the care of obstetrics. Briefly stated these are:

A. Obstetrics must be handled in a portion of the hospital completely separated from that devoted to the care of other patients.

B. The personnel handling the obstetric case, particularly the nurses, must have no part in the care of other patients.

C. The hospital must be responsible for supervising the care the obstetric patient receives, ensuring adequate professional treatment.

In order to carry out these provisions, it is necessary that the nursing department of any hospital handling obstetrics shall have a trained obstetric supervisor with a sufficient number of nurse assistants so that they can handle the obstetric work without calling for help from other parts of the hospital. To fully meet this requirement places a serious economic problem on the smaller hospital. However, not to come up to this standard leaves the institution an unsafe place for obstetric care.

During 1936 and 1937 committees of the Hospital Obstetric Society of Ohio visited practically every hospital in the State having as many as 100 deliveries a year. The report of the chairman, Dr. S. R. Burlage, was presented at a joint meeting of the Ohio Hospital Association and the Hospital Obstetric Society of Ohio at Columbus, in April, 1937. This report was approved, and endorsed by both organizations. The following is quoted from this report: "For safe obstetrics there can be but one standard, regardless of the type of institution in which the work is carried on. In the obstetric division of any general hospital, regardless of size, absolute isolation of the division must be practiced. Physical isolation is not enough. There must be separate personnel, without interchange of person, laundry, or equipment; it must be a separate division in fact as well as in name. Any general hospital regardless of size must meet these demands to be authorized as a fit institution to be licensed to handle obstetric patients."

Let us consider what this standard requires of the small hospital. The minimum under which these nursing requirements could be met is to have one nurse on duty in the division with two nurses off duty, at least one of whom could always be called in an emergency. The volume of work necessary to employ one nurse would be at least four cases. The minimum hospital should, therefore, average an occupancy of four obstetric cases. If patients stay an average period of ten days this would mean slightly over 12 births a month or roughly 150 births a year.

This figure of 150 births a year has, therefore, been arbitrarily selected as the minimum number of deliveries with which proper obstetric standards can be



maintained. However, to denominate a hospital as a safe or an unsafe place for the handling of obstetric cases merely on the basis that it falls above or below the arbitrary standard of 150 deliveries in a given year is, on the face of it, absurd. All obstetricians whose experience extends to a number of smaller hospitals know that there are institutions in which the volume of work far exceeds this minimum figure in which the standards are woefully inadequate. They also know that there is an occasional hospital of this size, or slightly larger, which is meeting the requirements and rendering commendable service while being economically self-sufficient. On the other hand there are two types of institution that can give good service with less than the specified volume of work. Some small maternity hospitals that abide by the restriction inherent in their name, are well managed on a very low occupancy, and institutions that are endowed, or are willing and able to foot a temporary loss in order to give adequate service are, in a few instances, meeting the requirements with a volume of less than 150 deliveries a year. But, in general, it is safe to say that there are very few general hospitals with less than this minimum whose service to their clientele is adequate.

In order to make a statistical study some point of division had to be made, and, for the reasons given, the figure of 150 deliveries a year was chosen for the purposes of this study. The republication of a table from "An Obstetrical Audit"<sup>1</sup> which was the result of a study made with the help of the vital statistics department of the Ohio Board of Health will help justify the selection made (Table I).

TABLE I. PUERPERAL MORTALITY IN OHIO HOSPITALS

		NO. OF HOS- PITALS	BIRTHS	PUER- PERAL DEATHS	PUER- PERAL RATE
Hospitals approved					
For residencies	1937	17	19,169	119	6.22
	1938	22	25,401	109	4.29
For internships only	1937	22	14,777	98	6.65
	1938	21	14,374	68	4.74
Hospitals not approved for graduate train- ing					
Having more than 150 births a year	1937	40	12,898	119	9.23
	1938	45	14,380	107	7.45
Having less than 150 births a year	1937	66	4,304	78	18.10
	1938	73	3,886	73	18.80

These figures, which are but an expression of the opinion of many experienced obstetricians, prove beyond peradventure the inadequacy of the small hospital from an obstetric point of view. Instances could be cited, such as that of a hospital having 66 deliveries in one year during which there were 3 deaths following cesarean section and one following sepsis, but the figures in the table carry the point without elaboration.

In order to determine the extent of the problem which hospitals having less than 150 deliveries a year present, the following figures have been compiled from the 1938 reports of the Council on Medical Education and Hospitals of the American Medical Association.<sup>6, 7</sup> For the purposes of this study hospitals have been divided into five groups: (1) those having an average occupancy of about 200, which are listed as having over 7,000 admissions a year; (2) those having an average occupancy of between 100 and 200, listed as 3,500 to 7,000 admissions a year; (3) those having an average occupancy of from 50 to 100, listed as 1,750 to 3,500 admissions a year; (4) those having an average occupancy of from 25 to 50, listed as 875 to 1,750 admissions a year; and (5) smaller hospitals, listed as under 875

admissions a year. Each of these groups was then divided into those hospitals that had over 150 deliveries a year and those hospitals that had less than 150 deliveries a year.

In the two groups of hospitals having an average occupancy of over 100, the number of hospitals having less than 150 births a year, and the number of births occurring in them are very small. In the group having from 50 to 100 average occupancy, there is an increase in the number of hospitals with less than 150 births a year. In the group of hospitals having an average occupancy of between 25 and 50, the number of deliveries in hospitals with under 150 births a year reaches 24.5 per cent of the births in this group. And in the group of hospitals with an average occupancy of under 25, the births in hospitals having under 150 births a year reached 77.0 per cent of all the births occurring in that group. In this group of smallest hospitals there are 84 classified as "Maternity" hospitals, although not all of these restrict their work rigidly to obstetrics. Twenty-nine of these "Maternity" hospitals had over 150 deliveries, and 55 of them had less in 1938. There were no maternity hospitals in the larger groups of hospitals which had less than 150 deliveries a year. Hence, if we grant that the care in these 55 hospitals was acceptable, which is certainly not true of them all, and subtract this 55 from the total hospitals that did not have 150 deliveries, we are left with a total of 2,241 hospitals in which it is difficult to conceive that adequate obstetric care would have been possible. These 2,241 hospitals comprise over one-half (55 per cent) of all the hospitals doing obstetrics in the United States, although only 13.1 per cent of hospital deliveries occurred in them. The percentage of births occurring (Fig. 1) in hospitals of the less-than-150-births-a-year class varied from a percentage of 2.07 in Rhode Island to one of 59.3 in Mississippi. The percentage of hospitalization of obstetrics for each state is presented (Fig. 2) for comparison.

The efficiency of a hospital is considerably determined by the character of its house staff, composed of its residents and interns. This is particularly true when it comes to the management of the obstetric case. Aside from the assistance which this staff renders to the attending physician, which is a real aid to him, and therefore, a distinct benefit to the patient, these doctors are the agents of the hospital administration in meeting the third requirement of adequate obstetric management—the responsibility of the hospital for ensuring adequate professional treatment. The director of the obstetric department cannot personally keep constantly informed as to the status of each patient, but the house staff can bring any abnormal case to his attention. The value of any house staff obviously depends upon the type and amount of the training its members have had. A resident who has passed his first year of graduate training, is more to be relied upon than a first year intern. A department having both residents and interns is superior to one having only one type of service, and the most reliable obstetrical house staff is found in the hospital approved for obstetric residencies.

Examining hospitals from this point of view, we find that the two groups of hospitals having less than an average occupancy of 50 contain no institution approved for an obstetric residency and no institution that is approved for both residents (any type) and interns. Only 10 of the 2,687 hospitals in these two groups are approved for any type of graduate training.

In the next group of hospitals, those having an average occupancy of from 50 to 100, out of the 712 hospitals included, 10 are approved for both residents (any type) and interns and 8 for residencies only. In this group of 18 hospitals there are 5 approved for residencies in obstetrics or obstetrics-gynecology, 2 of them being specialized maternities and 2 hospitals for the colored. Five of the 18 hospitals in the group that have approved residencies do not have 150 deliveries a year. Of the total 712 hospitals of this size 127 are approved for internships only. The remaining 567 of these 712 hospitals are not approved for graduate training. In the two groups having an average occupancy of over 100, there are 1,169 hospitals, and in these hospitals 53.1 per cent of all hospital births occur.



Only 96 of these hospitals are not approved for some type of graduate training, and only 33 of them having a total of less than 1,000 deliveries, had under 150 births a year in 1938.

In hospitals that have insufficient staff organization to obtain approval for some type of graduate training it is unusual to find an organized obstetric department headed by a responsible chief of service. This situation also holds true in a number of hospitals approved for intern training only and in some hospitals approved for residencies other than obstetrics. Sometimes even when there is a nominal chief of the obstetric service in a hospital having an approved graduate training status, he, with the aid of his trained assistants, is not always given authority by the hospital to supervise the type of obstetric work carried on within its walls. It is obvious, therefore, that with regard to the kind of professional service that a hospital can offer, even taking the house staff only into consideration, the smaller hospital has difficulty in meeting the requirements of the supervisory bodies.

As shown elsewhere,<sup>1</sup> there has been in the last five years a decrease of 14.4 per cent in the number of hospitals having less than 150 births a year and a decrease of 5.5 per cent in the total births occurring in such institutions. But in spite of this reduction, this study reveals that the small hospital is still a significant factor in United States obstetrics.

In communities having sufficient density of population to ensure support of one or more hospitals able and willing to meet the obstetric requirements, the struggle to keep alive an inadequate obstetric department in a smaller hospital is rarely a service to the community. The problem of adequate obstetric hospitalization in the small town community that is often served by a small hospital is not an easy one. There are a few such small city hospitals in Ohio that have given careful thought to the problem. In each instance there is only one hospital in the vicinity, and it is too small to maintain a properly organized obstetric department. Their answer is home deliveries whenever the obstetric case is normal, but if an abnormal case presents, where surgery or major procedure is needed, that patient is admitted. The result is that comparatively few obstetric cases enter the hospital, seldom more than one at a time, and the contagion, if any, can be thoroughly eliminated before the next case is admitted. There is no risk of cross infection and yet the patient that badly needs hospital care is provided for. This is by no means an adequate solution of the problem, but in view of the lack of proper hospital facilities it is a workable makeshift.

It would be ideal if hospitals could be established in many areas which at present lack such facilities. But this would necessitate not only sufficient funds to build and equip these hospitals, but an adequate endowment to enable them to operate properly until the volume of business could carry the overhead. Further, these hospitals should be adequately staffed, not only with sufficiently trained nursing personnel, but with obstetricians of training. One of the chief reasons that the record of many small hospitals is poor is that the doctors available have not had sufficient experience in the varieties of obstetric complications and lack the breadth of view necessary for balanced judgment. If doctors of proper caliber were available, having at their disposal an adequate hospital plant, they would in all probability soon develop sufficient clientele to maintain the installation. It is difficult for such an ideal situation to develop spontaneously, but if such organizations were established and maintained for a time, they should prove practical in well-selected communities.

#### SUMMARY AND CONCLUSIONS

1. The hospital with less than 150 births a year is rarely maintained with the proper obstetric safeguards and is usually a hazard to the woman in childbirth.
2. Over one-half of the general hospitals in the United States are in this class and 13.10 per cent of all babies delivered in hospitals are delivered in hospitals of this type.

3. Hospitals in this grouping are becoming less numerous, but a disproportionately large number of puerperal deaths still occur in such hospitals.

4. The recognition of the hazard inherent in institutions of this type will hasten their elimination and assist in further lowering the obstetric death rate.

5. There are a large number of hospitals with good obstetric organization and the public and professional sentiment is furthering their increase.

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- (1) *Runnels, S. C.*: J. A. M. A. 113: 402, 1939. (2) *De Lee, J. B.*: The 1939 Year Book of Obstetrics and Gynecology, Chicago, 1940, p. 351 (and personal communication). (3) Manual on Obstetrical Practice in Hospitals, Chicago, American Hospital Association. (4) *MacEachern, M. T.*: AM. J. OBST. & GYN. 35: 535, 1938. (5) *Skeel, A. J.*: President's Address, Hospital Obstetric Society of Ohio, 1938. (6) Council on Medical Education and Hospitals, J. A. M. A. 112: 909, 1939. (7) Council on Medical Education and Hospitals, J. A. M. A. 113: 757, 1939.

9400 EUCLID AVENUE

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## Society Transactions

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### NEW YORK OBSTETRICAL SOCIETY

JOINT MEETING WITH THE OBSTETRICAL SOCIETY OF PHILADELPHIA AND  
THE BOSTON OBSTETRICAL SOCIETY, APRIL 9, 1940

The following paper was presented:

**Abdominal Pregnancy.** Dr. Clifford B. Lull, Philadelphia, Pa. (For original article, see page 194.)

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### PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF APRIL 1, 1940

The following papers were presented:

**Relation of Ovarian Function to Uterine Fibroids.** Dr. E. M. Baker.

**Ovarian Cyst With Twisted Pedicle.** Dr. E. F. Williams.

MEETING OF MAY 15, 1940

The following paper was presented:

**The Relation of Vitamin B<sub>1</sub> to the Reproduction Cycle. Correlation Between Vitamin B<sub>1</sub> Content of Diet and Electrocardiographic Findings in 91 Pregnant Women.** Drs. Philip Williams, G. C. Griffith, and F. G. Fralin, Philadelphia (by invitation). (For original article, see page 181.)



# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Physiology of Pregnancy

**Martzy, St., and Pap, K.:** The Pregnancy Test of Nito, *Klin. Wehnschr.* 17: 1084, 1938.

Nito recently described a new test for pregnancy for which results were claimed better than those with the Friedman test. Nito found that the injection of urine from pregnant women into the circulation of rabbits produced a marked and rapid leucopenia. Urine from nonpregnant women produced practically no change in leucocyte count.

The authors compared this test with the Friedman test in a series of 150 patients and found the test completely unsatisfactory and unreliable, there being a large percentage of false positives in conditions other than pregnancy. In addition, there were 9 negative tests among 30 early pregnancies and 3 negatives in 18 late pregnancies. The authors therefore conclude that the test should be discarded.

RALPH A. REIS.

**Chesley, Leon C., and Chesley, Elizabeth R.:** The Cold Pressor Test in Pregnancy, *Surg. Gynec. Obst.* 69: 436, 1939.

Hines and Brown have proposed the "cold pressor test" which measures the response of the blood pressure to the immersion of one hand in ice water.

Many writers believe that the toxemias of pregnancy, exclusive of true nephritis, are related to primary hypertension. Corwin and Herrick "incline to the view that the subacute, hypertensive toxemia of pregnancy is the response of the woman with latent or declared cardiovascular disease to the strain of pregnancy." If the cold pressor test enables one to pick out the patients with latent or potential cardiovascular disease, as Hines and Brown believe, then perhaps it would also enable one to detect patients likely to develop toxemia of pregnancy. This would be of great importance for the study of toxemia and might even be of some benefit to the patient.

In the present investigation, cold tests have been done in the third or early fourth month, again in the eighth or early ninth month and again six weeks or more post partum in 517 women.

The response to the cold test is inconstant. While many patients do give reproducible rises in blood pressure, others have given highly variable responses at different times.

The response to the cold test is independent of family history of cardiovascular-renal disease and diabetes. It is also independent of age, gravidity, weight, weight-height index, weight gain in pregnancy, and perhaps also the basal blood pressure.

The incidence of toxemia is essentially the same in both normal and hyperreacting groups. The frequency distribution of responses is essentially the same in both pretoxemic and "prenormal" groups.

WILLIAM C. HENSKE.

**Parsons, Susanne R.:** Evaluation of the Intradermal Test for Pregnancy, *Surg. Gynec. Obst.* 68: 187, 1939.

The intradermal skin test for pregnancy in 679 cases has proved entirely unreliable in the hands of all workers who have attempted to repeat the work of Gilfillen

and Gregg. There seems to be no choice among the various hormonal preparations used; all yield equally unreliable results.

WILLIAM C. HENSKE.

**Laves, W.: The Hogben Test for the Biologic Determination of Pregnancy,** Deutsche med. Wehnschr. 66: 5, 1940.

Laves discusses the technique of the Hogben test and describes the habits, care, and feeding of the African clawfrog *Xenopus laevis Daudini* which responds to the injection of gonadotropic hormone with ovulation. A morning specimen of urine of specific gravity 1.020 or greater is used. This is acidified if necessary to a pH of 5.5 and 1 or 2 c.c. is injected in the frog's dorsal lymph sac. The frog is then placed on a raised large-screen platform an inch or so above the floor of its glass cage. The reaction is generally determined in twenty-four hours. Absence of eggs gives a negative test, 20 to 50 eggs a weak positive, and 50 eggs or more give a positive test.

The findings in a case of adnexal inflammation mistaken for ectopic pregnancy and in a case of pregnancy of less than one month's duration are given.

R. J. WEISSMAN.

**D'Erchia, F.: Another Anatomical Report in Favor of Endouterine Nidation of the Human Ovum,** Riv. ital. di ginec. 20: 463, 1938.

Based on a study of a case of placenta succenturiata, the author affirms that its development occurred upon the decidua reflexa but not upon the decidua serotina, which is deprived of function, less vascular and contains less mucosal glands than the decidua reflexa.

These findings confirm his opinion expressed in a previous paper that the incubating chamber of the human ovum must be considered not as an intradecidual space but as the integral part of the uterine cavity.

AUGUST F. DARO.

**Gorman, William A., and Hirsheimer, A.: A Study of the Superficial Venous Pattern in Pregnant and Non-Pregnant Women by Infra-Red Photography,** Surg. Gynec. Obst. 68: 54, 1939.

The regions photographed by means of infrared rays were the trunk anteriorly and posteriorly and, in a few cases, laterally, and the lower extremities anteriorly and posteriorly.

The following observations were made: No changes occurred in the superficial veins of nonpregnant women during the menstrual cycle. There were no demonstrable differences between the changes in the venous patterns of normal pregnant women and those of pregnant women with organic heart disease or toxemia.

There is an increase in the prominence of the veins of the breasts early in pregnancy, noticeable at the third week, and very definite at the eighth week. At the time of the first noticeable increase in the veins, there is also a noticeable increase in the size of the breasts.

There is an increased prominence of the abdominal venous pattern first noticeable at about the fifth month when there is obvious enlargement of the abdomen.

It is not possible to state from the appearance of the veins whether or not the subject is a primigravida or a multigravida.

Definite changes are limited to the venous pattern of the anterior trunk. There is a marked dissimilarity of venous patterns among all the subjects photographed.

The changes in the prominence of the veins are principally due to the stretching and thinning of the overlying tissues. It is probable that an increase in blood content, and in the case of the breasts, of physiologic hyperemia contribute to the effect.

WILLIAM C. HENSKE.

**Patat, P.: Relations Between Ocular Tension and Pregnancy, Zentralbl. f. Gynäk.** 62: 868, 1938.

Comparative tests on nonpregnant women of the same age revealed that the ocular tension of pregnant, parturient, and puerperal women is usually reduced. In 27 women in whom the values had been found definitely reduced during pregnancy, the author renewed the test one or two years after delivery. The presented tabulation clearly demonstrates that the ocular tension of the same person is usually lower during the processes of gestation than is the case one or two years after delivery. Discussing the possible cause of the ocular hypotension during pregnancy, the author suggests first that the acidosis of pregnancy might play a part, pointing out that a lowered ocular tension has been observed during other processes that are accompanied by acidosis, such as diabetic coma. Other factors that might be involved are reduction in the osmotic pressure, chemical changes in the blood, or changes in the endocrine function. A complete explanation has not been found as yet.

J. P. GREENHILL.

**VanLiere and Sleeth: The Question of Cardiac Hypertrophy During Pregnancy, Am. J. Physiol.** 122: 34, 1938.

On the basis of their investigations on guinea pigs, cats and dogs, the authors maintain that pregnancy does not cause cardiac hypertrophy in these animals. Since pregnancy does not produce cardiac hypertrophy in three different types of animals, it seems doubtful that it would produce it in human beings. Increased cardiac work does not necessarily produce cardiac hypertrophy.

J. P. GREENHILL.

**Bortolucci, P.: The Detoxicating Function of the Liver During the Puerperal State, Riv. ital. di ginec.** 20: 445, 1938.

Using santonine as an hepatic toxic agent to test the detoxicating function of the liver of pregnant women, the author concludes that pregnancy acts to reduce the antitoxic quality of liver function.

AUGUST F. DARO.

**Ramsay, Thierens, and Magee: The Composition of the Blood in Pregnancy, British M. J.** 1: 1199, 1938.

The hemoglobin, the bactericidal power of the blood against hemolytic streptococci, and the calcium, inorganic phosphorus, and phosphatase contents of the serum were studied in 101 women at the seventh month of pregnancy.

Seven per cent were found to be definitely anemic and 19 per cent probably slightly so. In 39 per cent, the calcium level was less than 9 mg. per 100 ml., which is believed to be abnormally low. The product calcium  $\times$  phosphorus was 25 on the average. The blood of 22 patients failed to inhibit the growth of streptococci and, of these, one developed pyrexia during the puerperium; fever also occurred in a patient whose blood inhibited growth at the seventh month.

The literature reveals that the serum calcium and phosphorus fall and the serum phosphates rise gradually as gestation advances.

F. L. ADAIR AND S. A. PEARL.

**Pitts and Packham: Hematology of Sternal Marrow and Venous Blood of Pregnant and of Nonpregnant Women, Arch. Int. Med.** 64: 471, 1939.

Of 40 pregnant women attending the outpatient maternity clinic of the Vancouver General Hospital none had a past history suggesting a blood dyscrasia, and all of them were found by consideration of the history and by physical examination to be in good health. For comparison, studies were made on 24 healthy nonpregnant women of about the same age.

It was found that the erythrocyte counts and hemoglobin estimations for pregnant women are 10 to 15 per cent lower than for healthy nonpregnant women of the same age group. The hemoglobin and akaryocyte (nonnucleated erythrocyte) counts for the sternal marrow in pregnancy are somewhat lower than the corresponding counts for the blood. The leucocyte counts of the blood during pregnancy are significantly higher than for healthy nonpregnant women. The total nucleated cell counts for the marrow are definitely higher in pregnant than in nonpregnant women. It is noteworthy that there is no decrease in any of the nucleated erythrocytes during pregnancy, which indicates that the physiologic anemia of pregnancy is due not to decreased erythrocyte production but, as others have shown, to the increase in plasma volume. There is even a slight increase in the reticulocyte counts during pregnancy, suggesting that there may be a slightly increased rate of erythrocyte formation.

J. P. GREENHILL.

**Cetroni, M. B.: Fetal and Maternal Polypeptidemia, Riv. ital. di ginec. 22: 429, 1939.**

By the method of Cristol and Puech, the author determined the polypeptidic azote contents in blood serum of 18 healthy, nonpregnant women (average mg. 2.88 per cent) and of 48 pregnant women from the fourth month to full term.

He observed a progressive increase of polypeptides during pregnancy (average mg. 3.66 per cent up to fourth, fifth and sixth months; mg. 4.17 up to seventh and eight months; mg. 4.85 per cent up to ninth month and at term).

Researches at the same time carried out for the fetus showed that the level of polypeptides in the fetal blood serum is always higher than the maternal, averaging: mg. 3.87 per cent for the fetus up to fourth, fifth, and sixth months; mg. 4.49 per cent up to the seventh and eighth months; and mg. 5.81 per cent up to the ninth month and at term.

The polypeptidic azote in the blood serum of the umbilical vein is always higher than that in the blood serum of the umbilical arteries (respectively, mg. 6.14 and mg. 4.92 per cent).

The fetal polypeptidemia is higher than the maternal, because in the cord blood are not only the polypeptides of the maternal blood but also those that originate from the action of proteolytic placental ferments.

The higher contents of polypeptides in the blood of the umbilical vein as compared with the arteries might be a proof of the utilization by the fetus of the polypeptides that are derived from the placenta, and might indicate action of the fetal liver in the synthesis of the azoted substances.

In the blood of the newborn child the level of the polypeptides diminishes rapidly. This is probably due to the sudden suspension of transplacental passage of polypeptides.

AUGUST F. DARO.

**Quinto, Pietro: Phosphatase During the Puerperium, Riv. ital. di ginec. 22: 347, 1939.**

The author studied with the method of Jenner and Kay the behavior of the plasma's phosphatase contents during the various periods of pregnancy, labor and puerperium. He found that in pregnancy phosphatase increases progressively until it reaches the maximum values during the last month and in labor, after which it returns to the normal level within the first ten days of the puerperium.

The author determined that the phosphatase contents of the fetal blood at the time of birth are relatively high but always less than those of the mother's blood.

AUGUST F. DARO.

**Elmby and Christensen: Ascorbutic Acid in Pregnancy, Labor, the Puerperium and the Neonatal Period, Klin. Wehnschr. 17: 1432, 1938.**

The authors' studies were carried out in 500 women during the last five months of pregnancy, during labor, and throughout the puerperium. Determinations were

made of the acid content of the blood, urine, milk as well as of the umbilical cord blood and blood from the ear of the newborn infant. A direct relation was found between the acid intake and the acid level of the blood, and of the milk. The levels found during the latter half of pregnancy were definitely below those of the non-pregnant. The acid level of the newborn infant approximates that of the mother and is dependent upon it. The level sinks rapidly during the first ten days of life. Increasing the oral intake during the puerperium will maintain serum and milk levels at the normal nonpregnant level. The authors conclude that the usual winter rations of Germany are markedly deficient in vitamin C.

RALPH A. REIS.

**Grossi, Giuseppe: Relation Between the Elimination of Ascorbutic Acid in the Urine and Interruption of Pregnancy, Folia dermatograph. gynaec. 36: 328, 1939.**

The author studied the excretion of vitamin C in its relationship to pregnancy in a group of patients, particularly concerning probable interruption of pregnancy.

It seems that in patients with threatened abortion, ascorbutic acid content is lowered in the urine. The author studied in all 32 cases where the threatened interruption did not terminate in abortion and seven patients in whom the threatened interruption continued to abortion.

In the first group the average ascorbutic acid content of the urine was 4.7 mg. per 100 c.c. while in the latter group this content averaged 2.3 mg. per 100 c.c. He found that in normal pregnancy the average ascorbutic acid content of the urine was 4.1 mg. per 100 c.c.

MARIO A. CASTALLO.

**Sadovsky, A., Weber, D., and Wertheimer, E.: Concentration of Vitamin C in Blood During and After Pregnancy, J. Lab. & Clin. Med. 25: 120, 1939.**

Determinations of vitamin C in the blood were made immediately upon withdrawal of the blood in 222 women. The average concentration was 1.01 mg. per cent. There were several interesting findings. The vitamin C concentration was highest during pregnancy; lowest after confinement. The highest values were found during the citrus fruit season. During hyperemesis gravidarum, a secondary decrease in vitamin C was noted, but substitutive administration of the vitamin in one case had little effect on the hyperemesis.

R. J. WEISSMAN.

**Nixon, J. A.: Diet in Pregnancy, Bristol Med.-Chir. J. 56: 165, 1939.**

Discussing dietary influences on gestation, Nixon concludes that much more investigation must be done on the effects of modifying the diets of expectant mothers. Well-fed mothers appear to be less liable to puerperal sepsis. In 48,881 cases studied by the Joint Council of Midwifery, the infant mortality (stillbirths plus neonatal) per thousand was 59 for mothers receiving special foods, puerperal sepsis accounting for 0.26 mothers per thousand. Mothers not receiving special foods, but attending antenatal clinics, had an infant mortality rate of 71; sepsis deaths 0.67 per thousand. Those not attending clinics and not obtaining special foods had an infant mortality of 92; sepsis deaths 0.88 per thousand.

The importance of the various elements of the diet is discussed in detail. The average caloric requirement of an active nonpregnant woman is given as 2,500 calories per day. In pregnancy this should be gradually increased after the fourth month to a 20 per cent increase over the above figure. The League of Nations Technical Commission recommends a diet yielding 3,440 calories and gives the daily requirements of protein, 105 Gm.; calcium, 1.6 Gm.; phosphorus, 2.0 Gm.; iron, 10.2 mg.

R. J. WEISSMAN.



**Valentinuzzi, Maximo: The Physics of the Gravid Uterus: Its Pressure, Tension, Tone, Contractions, and Labor, Rev. méd. latino-am. 284: 290, 1939.**

Summarizing his studies the author states that mathematical analysis of forces that participate in the uterine mechanism of labor permits to establish some quantitative relations between myometrium shortening and intrauterine pressure (Weber-Wolf's law), between tension of the uterine wall and intrauterine pressure (Barrau-De Snoo's law), between myometrium shortening and uterine tension, between amplitude of the contraction and uterine tension, and between expulsive work and intrauterine pressure. All of these relations offer one further step toward a rational systematization of the knowledge about the uterus during labor. The electrical theory of muscular activity introduces the concept that tone and contraction depend on the same physical mechanism, that is, on electrical charges, so that it seems correct to state that *tone is a function of contractility*. This interpretation does not deny the experimental facts which characterize tone and contraction, but they are included and explained in it. The variation of the uterine muscular tension, either as tone or as contraction when the other factors remain unchanged, depends on a change in the intramuscular charges produced by physiologic (hormonal, biochemical, nervous) or pharmacologic stimuli. In this sense, oxytocic substances would elevate the electrical charge of the myometrium and sedative substances would diminish it.

MARIO A. CASTALLO.

**Siegler, S. L.: Estrogenic and Chorionic Gonadotropic Hormone in Pregnancy, J. Lab. & Clin. Med. 24: 1277, 1939.**

In an interesting report, Siegler compares the urinary estrogen and chorionic gonadotropin in five normal and one toxemic pregnancies. Findings in the case of toxemia at sixth or seventh month of pregnancy indicated the presence of an excessive amount of anterior pituitary-like substance, with a concomitant decrease of total estrogen to term. Twelve days before confinement the urine contained 31,700 R.U. estrogen and 49,000 M.U. of gonadotropic hormone. The patient had hydrops, generalized edema, severe headache, epigastric distress, and nausea; 1,000,000 I.U. of estradiol benzoate were given over the following ten days, with subsidence of symptoms and a change in the urinary endocrine picture to 52,000 R.U. estrogen and 12,000 M.U. gonadotropic hormone.

Five normal cases showed an average increase of estrogen from 3,500 R.U. thirty days after the first missed period to a peak of 82,000 R.U. at term. Gonadotropic hormone normally rose from 7,500 M.U. on the fourteenth day after the first missed period to 40,000 M.U. on the thirtieth day, with a rapid decline to levels of 10,000 M.U. decreasing evenly to 4,500 M.U. at term, and being absent four days post partum.

The author found that serum concentrations of hormones coincided with their concentration in the urine. He feels that the variations found in toxemia may possibly be the result of the visceral lesions found clinically in eclampsia and pre-eclampsia.

R. J. WEISSMAN.

**Lubin, Samuel, and Waltman, Richard: Results of Attempted Induction of Labor with Estrin, Surg. Gynec. Obst. 69: 155, 1939.**

Estrin can initiate and maintain uterine motility and contractility in animals and human beings. Experimental evidence has been cited to show that pregnancy in certain animals can be terminated by estrin administration.

The reports of successfully induced labor by estrin in the human being are inconclusive, because in practically all instances estrin was employed along with other procedures or substances which might in themselves produce labor.

The authors attempted to induce labor near, at, and beyond term by administration of estrin without additional aid. Of 36 patients employed in the investigation, it is possible that the onset of labor could be attributed to the injected estrin in 8 cases. It is also possible that the estrin might have been responsible for the

short labors in 4 of the 9 primiparas in this series. The onset of labor bore no relationship to the dosage of estrin employed.

The findings merely suggest the possibility that labor in the human being near, at, and beyond term might be induced by estrin administration and that duration of labor might be shortened by this method.

WILLIAM C. HENSKE.

**Wiessman, A.: Calculation of the Duration of Pregnancy,** *Klin. Wehnschr.* 17: 1611, 1938.

The author studied the duration of pregnancy in 5,000 consecutive deliveries and the relation of this duration to the type of menstrual cycle. It was found that the average duration of pregnancy was 280 days. Furthermore there was no demonstrable relation to the type of menstrual cycle, since the length of pregnancy was the same whether the pregnancy was in a woman with a 26-, 28-, or 35-day cycle. The author sees no reason to discard the Naegele rule for calculating from the first day of the last menstrual cycle by subtracting three months and adding eight days. He proves that the method is most accurate.

RALPH A. REIS.

**Kreis, J.: Prolonged Pregnancy or Late Fecundation,** *Rev. franc. de gynéc. et d'obst.* 33: 120, 1938.

Kreis believes that the normal duration of pregnancy in women who menstruate every twenty-eight days is not 280 days but 285 days on an average. In most cases of supposedly long pregnancy, the duration of pregnancy is actually normal but fecundation took place late in the menstrual cycle. That fecundation may take place late in the cycle is evidenced by the fact that ovulation can take place from the eighth to the twenty-seventh day. Hence, in cases where labor is supposedly overdue, we should not be anxious to induce labor.

J. P. GREENHILL.

**Bernhart, F.: The Duration of Pregnancy and Its Seasonal Influences,** *Monatschr. f. Geburtsh. u. Gynäk.* 107: 215, 1938.

The author studied 4,000 labor cases and came to the conclusion that the season of the year plays a role in the duration of pregnancy. He found that there was a slight increase in the number of prolonged pregnancies in summer and also a diminution in the number of short pregnancies during this time. However because of the small number of cases, no decisive conclusions can be drawn.

J. P. GREENHILL.

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## Books Received

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AN INTRODUCTION TO MEDICAL MYCOLOGY. By George M. Lewis, M.D., associate and assistant attending dermatologist, New York Post-Graduate Medical School, Columbia University, etc., and Mary E. Hopper, M.S., assistant in mycology, Skin and Cancer Unit, New York Post-Graduate School. 315 pages, 71 figures. The Year Book Publishers, Inc., Chicago, Ill., 1940.

EL DIAGNOSTICO PRECOZ DEL EMBARAZO. Par Dr. Carlos Colmeiro Laforet. 244 pages, illustrated. Libreria "Gali," Santiago de Compostela, 1940.

TEXTBOOK OF HISTOLOGY. By Harvey Ernest Jordan, professor of anatomy and director of anatomical laboratories, University of Virginia. Eighth edition, 690 pages, 609 illustrations. D. Appleton-Century Co. Inc., New York, 1940.

## Announcement

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The October issue of the JOURNAL will commemorate the twentieth anniversary of its establishment as an organ of publication in the domain of American obstetrics and gynecology. This special issue will present a series of brief, critical articles by a selected group of contributors, based on the developments during these past two decades in the fields to which the JOURNAL has been devoted.

We bespeak the attention of our readers to this anniversary number.

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## Item

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### **American Board of Obstetrics and Gynecology, Inc.**

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 4, 1941, at 2:00 P.M. Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.

Applications for admission to Group B, Part I, examinations must be on file in the Secretary's office not later than October 5, 1940.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Cleveland, Ohio, immediately prior to the 1941 meeting of the American Medical Association.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh, (6) Pennsylvania.